FINAL REPORT ON

NITRITES AND NITROSAMINES

REPORT TO THE SECRETARY OF AGRICULTURE

BY

THE EXPERT PANEL ON NITRITES AND NITROSAMINES

February 1978
Food Safety and Quality Service
U.S. Department of Agriculture

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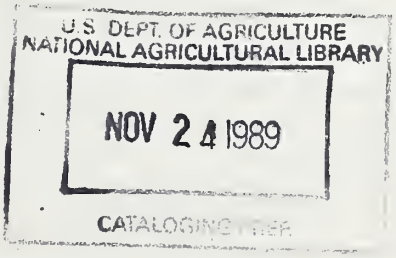

Historical Perspective

The curing of meat and meat products is generally understood to mean the perfusion of meats with common salt, nitrate, nitrite, sugar and spices. These curing ingredients work together to produce changes in the product resulting in extended stability and distinct color and flavor characteristics.

The curing of meat and poultry products today is based partly on the art as practiced over thousands of years and partly on scientific principles developed within the last 80 years. Meat was first preserved with salt as the curing agent in the saline deserts of Hither Asia and coastal areas. These desert salts contained nitrates as impurities. Even in Homer's time (900 B.C.), curing meat with salt, followed by smoking, was an established practice. Cato (234-149 B.C.) wrote careful instructions for dry-curing hams. It included rubbing with salt, overhauling with salt, rubbing with oil, smoking and rubbing the ham again with a mixture of oil and vinegar. However, it was not until Roman times that the reddening effect now attributed to nitrite was mentioned. The Romans had learned from the Greeks the technique of curing pork and fish with salt, and they were probably the first to establish a trade market for cured meats. Meat cured with salt containing nitrate, and even nitrite impurities, developed a characteristic cured flavor and color, as well as the properties of a preserved product.

Chemists and meat scientists in the early 1900's determined that the active agent responsible for the color and flavor changes was nitric oxide, formed from nitrite which in turn was formed from the nitrate used in the cure. Because the extent of these reactions was difficult to control, the Department in 1925 formally authorized the direct addition of nitrite.

In accepting the use of nitrite in 1925, the Meat Inspection Division also recognized the acute toxicity aspects of nitrite and therefore established a maximum allowable residual of nitrite of 200 parts per million. Nitrate was not directly regulated.

In 1962, outbreaks of toxic hepatosis occurred in ruminants in Norway. Investigations indicated a connection between the disease and herring meal feed preserved with sodium nitrite. Investigators later demonstrated that dimethyl-nitrosamine was produced in the fish meal as a result of certain processing plants adding nitrite to the fish as a preservative and then drying the fish at high temperatures. Nitrosamines had previously been identified as a class of compounds, many of which were potent carcinogens.

In 1963, the U.S. fish industry was economically depressed, partially as the result of three separate outbreaks of botulism. The smoked fish

industry was particularly affected. Ways to protect both products and consumers were studied by scientists from the U.S. Bureau of Fisheries and the Food and Drug Administration, who developed the nitrite technology. However, in 1971 when the use of sodium nitrite in smoked whitefish came before the Food and Drug Administration, continuing concern over the nitrosamine problem led to the requirement for residual nitrosamine studies in cured fish. These studies showed that low levels of nitrosamines were formed in certain species of nitrite-cured fish. This led the scientific community to investigate for the presence of nitrosamines in cured meat products.

In the late 1960's questions were raised as to the use of nitrites in food and their combination with other compounds in the food or in the body to form nitrosamines. In October 1969, meat industry scientists met with the Assistant Secretary of Agriculture to discuss the possibility of a nitrosamine problem existing in U.S. cured meat products. In December of 1969, a group of USDA, FDA, and industry scientists met to discuss the problem, resulting in the scheduling of a cooperative research program to be funded by industry and actively participated in by industry, FDA, and the Department. The Food and Drug Administration (FDA) and the U.S. Department of Agriculture organized a scientific study group to review appropriate information and data. In 1971, the House Intergovernmental Relations Subcommittee conducted hearings on the issue of nitrosamine formation and the possible involvement of nitrite in cured foods. The matter was widely discussed by the public and the media, and further studies were carried out by the scientific community. Numerous conferences were held during 1972, to discuss available information on the role of nitrite in curing and preserving, and to determine what new information was needed.

Early in 1972, the Department was petitioned to ban or greatly reduce the amount of nitrite used in the curing process. The Department denied the petition, indicating additional information was needed on the chemistry associated with nitrosamine formation. Another factor associated with the problem was the recognized role of nitrite in inhibiting the growth of Clostridium botulinum. These bacteria, under favorable conditions, can produce the deadly toxin responsible for the food poisoning known as botulism. Information in literature indicates that in the 1920's scientists were demonstrating the antimicrobial effect of nitrite, and further investigation continued through the years. In the early 1970's, concentrated research studies were begun to learn more precisely the antimicrobial role of nitrite in modern forms of meat products. Sufficient data were gathered to satisfactorily substantiate the inhibitory action of nitrite to the growth of Clostridium botulinum.

Because of the widespread interest in the subject, the Secretary appointed an Expert Panel in 1973 to assess the data concerning the presence of nitrosamines in foods, to evaluate the public health significance and specific problems identified with the use of nitrites in

foods, and to determine if alternate methods of processing were available.

The Panel held 15 meetings during the period 1973-1977 during which it heard and evaluated testimony on the problems associated with nitrosamine formation and the use of nitrate and nitrite in cured meats. Recommendations were made in 1973; an interim position paper was prepared after the Panel's November 1976 meeting; and final recommendations were made at the last meeting in September 1977. Membership in the Panel changed substantially over the years and reference is made to Page 4 for an outline of those changes.

Members of the
Expert Panel on Nitrites and Nitrosamines

Note: Listed officials of the Department from Washington, D.C., were non-voting members of the Panel.

Members of the Panel at the last meeting, September 1977.

Chairperson
Ms. Carol Tucker Foreman
Assistant Secretary of Agriculture
Food and Consumer Services

Vice Chairman
Robert Angelotti, Ph.D.
Administrator, FSQS

Secretary
Irwin Fried
Director, Product Labeling and Standards, FSQS

Dr. Cecile H. Edwards (Feb. 1974 - Sept. 1977)
Dean, School of Human Ecology
Howard University
Washington, D.C.

Dr. Hans L. Falk (May 1977 - Sept. 1977)
Director, Office of Health Hazard Assessment
National Institute of Enviromental Sciences
Research Triangle Park, NC

Dr. Richard Greenberg (Feb. 1974 - Sept. 1977)
Director of Research
Swift and Company
Chicago, IL

Dr. Michael Jacobson (May 1977 - Sept. 1977)
Executive Director
Center for Science in the
Public Interest
Washington, D.C.

Dr. James P. Keating (Feb. 1974 - Sept. 1977)
Associate Professor of Pediatrics
Director, Division of Gastroenterology
Director, House Staff Training
St. Louis Children's Hospital
St. Louis, MO

Dr. William Lijinsky (May 1977 - Sept. 1977)
Director, Chemical Carcinogenesis Program
Frederick Cancer Research Center
Frederick, MD

Dr. Sidney Mirvish (May 1977 - Sept. 1977)
Professor, Epply Institute for Research in Cancer
University of Nebraska Medical Center
Omaha, NE

Dr. Robert Schaffner (March 1975 - Sept. 1977)
Associate Director for Technology
Bureau of Foods
Food and Drug Administration
Washington, D.C.

Dr. A. E. Wasserman (Feb. 1974 - Sept. 1977)
Chief, Meat Laboratory
Eastern Regional Research Center
Philadelphia, PA

In addition to the above, the following also served on the Panel:

Chairman
Dr. Richard Feltner
Assistant Secretary of Agriculture
Marketing and Consumer Services

Vice Chairman
Dr. Harry C. Mussman
Associate Administrator
Animal and Plant Health Inspection Service

Secretary
Dr. Richard Alsmeyer
Meat and Poultry Inspection, APHIS

Dr. Leo Friedman (Feb. 1974 - June 1974)
Director, Division of Toxicology
Food and Drug Administration
Washington, D.C.

Dr. John Weisburger (Feb. 1974 - Nov. 1976)
Vice President for Research
Naylor Dana Institute for Disease Prevention
New York, NY

Ms. Ellen Zawal (Feb. 1977 - Aug. 1977)
Zawal Associates
New York, NY

Ms. Carol Sundberg-Werner (Feb. 1977 - May 1977)
Professor, University of Wisconsin
Stout, WI

Final Report and Recommendations of the Secretary's Panel on Nitrites, Nitrates, and Nitrosamines

A majority of the members of the Expert Panel on Nitrites, Nitrates, and Nitrosamines have agreed that the following recommendations be made to the Secretary of Agriculture. Some members disagree with one or more of the recommendations and/or wish to comment on them or suggest changes or additions. These minority reports follow in the next section. In addition, initial recommendations (December 1974) and an interim position paper (November 1976) are appended to this Report.

Recommendation 1

The Secretary should publish a recommendation in the Federal Register establishing the amounts of ingoing and residual sodium nitrite, sodium nitrate, and sodium ascorbate/isoascorbate to be used in each class of cured product. (See Table.)

Recommendation 2

Not enough evidence has been produced to form a definite conclusion on the use of ascorbate/isoascorbate in any cured product, except bacon. Since these compounds have a proven blocking effect against nitrosamine formation in bacon, their use at the same levels should be made mandatory in other cured meats until data demonstrate a need to alter that level or discontinue its use.

Recommendation 3

Because there are insufficient data on the presence or absence of nitrosamines in most of the meat products shown in the attached Table, USDA shall request that data on nitrosamine formation during processing or preparation for eating be accumulated and submitted to the Department on a regular basis for a period of approximately 2 years.

In the proposal, USDA should request the details of the protocol for the determination of nitrosamines, and the Department in the final rulemaking should then specify the official method for determining nitrosamines. At this time, the best method for analysis of nitrosamines uses gas chromatography. Confirmation of nitrosamines is by mass spectrometric analysis.

Recommendation 4

If there is C. botulinum outgrowth in any of the products, the Department shall take immediate steps to halt its production and will allow revised processing procedures or increased levels of nitrite to be tested. Data must be obtained to establish the current occurrence of Clostridia and C. botulinum organisms in commercial products at the retail level.

Recommendation 5

For any product where carcinogenic nitrosamines are formed during processing or preparation for cooking or eating, the nitrosamine content should be closely monitored and reduced to an undetectable level as rapidly as possible; e.g., within 3 years.

Recommendation 6

The Department should take no immediate action on nonvolatile nitrosamines, but should monitor the course of current research.

Recommendation 7

USDA should monitor and support research on various other methods of preservation and propose adoption of their use when they have been adequately tested and approved.

Recommendation 8

A positive program should be developed by the Department of Agriculture for obtaining epidemiological evidence relating consumption of bacon and other cured meats to cancer incidence.

PANEL RECOMMENDATIONS CONCERNING SODIUM NITRITE, SODIUM NITRATE, SODIUM ASCORBATE/ISOASCORBATE USAGE AND RESIDUAL SODIUM NITRITE IN VARIOUS CURED MEAT PRODUCTS

	Products which are canned, cured, and:			Bacon	Cooked Ssusages	Other Pickle Cured Products	Dry Cured Cuts	Dry, Semi-dry and Fermented Sausage	Infant - Toddler Infant, Junior and Toddler Foods
	Perishable (canned ham)	Shelf stable (corned beef)	Commercially sterile (deviled ham)		(frankfurters)	(smoked ham)	(country ham)	(Lebanon bolognas pepperoni)	
Ingoing sodium nitrite (target level)[2]	156 ppm	156 ppm	50 ppm	120 ppm	100 ppm	156 ppm	100 ppm	100 ppm	0 [1]
Ingoing sodium nitrate (target level)[2]	0	0	0	0	0	0	300 ppm [3]	0 [3]	0 [1]
Ingoing sodium ascorbate or isosscorbate (target level)[2]	550 ppm [7]	550 ppm [7]	[6]	550 ppm	550 ppm [7]	550 ppm [7]	[6]	[6]	0 [1]
Maximum residual sodium nitrite at time of manufacture*	125 ppm	125 ppm	[4]	80 ppm	[5]	125 ppm	[6]	[6]	0 [1]

*USDA will set maximum residual sodium nitrite levels at appropriate time after manufacture if it is deemed necessary for protection of public health.

1/ In the meat portion of any infant, junior, or toddler food product.

2/ In the proposed rulemaking, USDA will present acceptable ranges around target level.

3/ The manufacturer may present data to USDA showing need for more sodium nitrate and safety of requested levels from nitrosamine formation in product.

4/ USDA to set level in proposal, but less than 50 ppm.

5/ USDA to set level in propoaal, but less than 100 ppm.

6/ Insufficient data available at this time to make any recommendation.

7/ Insufficient evidence presented to the Panel, although indications are that its role as a blocking agent would be similar to that in bacon.

Minority Reports of Panel Members

STATEMENT BY DR. CECILE EDWARDS

Issue 5: Interim and long term recommendations concerning bacon.

Nitrosamines, especially nitrosopyrrolidine--a potent carcinogen in laboratory animals, are consistently found in bacon treated under home conditions associated with frying and also in the rendered fat.

The rendered fat from bacon is frequently added to vegetables as a seasoning during the cooking process, and thus serves as a source of nitrosamines when such foods are ingested. The use of raw bacon, instead of bacon fat, would minimize this hazard.

In addition, rendered bacon fat is frequently used in the home for preparation of gravy for meats and the frying of food, including meats, fish and vegetables, such as potatoes.

THEREFORE, IT IS RECOMMENDED:

That the Secretary of Agriculture cause to be announced that the risk of cancer is increased when fried bacon or the rendered fat from it is consumed.

Drs. Jacobson, Lijinsky, Schaffner, and Falks endorse this statement.

STATEMENT BY DR. MICHAEL JACOBSON

The Expert Panel on Nitrite and Nitrosamines have recommended substantial reductions in the use of nitrite and nitrate in processed meats. If adopted by the Department of Agriculture as official regulations, these recommendations should significantly reduce the potential for nitrosamine formation in and the cancer risk associated with cured meats.

However, I believe that the Panel did not reduce the risk of nitrosamine formation to the minimum that is technically possible and economically feasible. Therefore, I am submitting the following comments and recommendations:

1. Nitrite is not necessary as a preservative in canned, cured, sterile, comminuted meat. If nitrite is to be used as a coloring and flavoring, the minimum amount necessary should be used. This is closer to 20 ppm than 50 ppm.

2. It was reported to the Panel on May 31, 1977, that a major meat processor (Briggs) used 79 ppm nitrite in at least one batch of bacon. Though this level of nitrite (in conjunction with 383 ppm

ascorbate) still led to the formation of nitrosamines, it apparently was effective as a preservative. The maximum level of nitrite in bacon should be 120 ppm, with the minimum being 80 ppm.

3. As long as bacon is made with nitrite, and nitrosamines form during cooking, the public deserves to be warned by appropriate label notices. Thus, people who wish to reduce their exposure to cancer-causing substances will be able to do so more easily. USDA should require the following notice to be printed on the principal display panel of all bacon packages: "NOTICE: CANCER-CAUSING CHEMICALS MAY FORM WHEN THIS BACON IS COOKED."

4. Manufacturers should be permitted to use less nitrite than the levels suggested by this Panel or that will be required by USDA, provided they demonstrate that the alternative methods of preservation they plan to use will result in safe products. USDA should encourage the development of processes that reduce or eliminate the use of nitrite and should then require the use of such processes.

5. The excessive consumption of sodium by some persons contributes to increased blood pressure, which increases the risk of heart attack and stroke. USDA has an opportunity to reduce sodium consumption by requiring the partial substitution of sodium nitrite, sodium chloride, and sodium ascorbate (or erythorbate) in cured meats by their potassium salts. USDA should work closely with FDA in reducing sodium levels so as not to introduce excessive levels of potassium in the diet. The total substitution of potassium nitrite and potassium nitrate for the sodium salts would lead to an increase of only about 35 mg of potassium to the daily diet of a heavy consumer of cured meats (five times the average amount).

6. A growing body of evidence indicates that nitrosamines can form in the stomach as well as in nitrite-containing foods. Indeed, at least one *in vivo* study demonstrates that nitrosamines form in the stomach following the ingestion of cured meat (IARC Scientific Publications No. 14, 1976, page 181). This finding adds urgency to the need to minimize human exposure to nitrite. Depending on the product, various alternatives to nitrite are available, including chemical preservatives, freezing, and reduction of water activity. Despite the importance of further research, industry has done very little. To protect the public from continued exposure to nitrite and nitrosamines, and to spur innovative and vigorous industry efforts, USDA should ban the use of nitrite in cooked sausages, bacon, and hams, except for low levels (10-20 ppm) that would fulfill the coloring and flavoring functions of nitrite. USDA should allow a 1-year grace period to give industry an opportunity to switch to other methods.

STATEMENT BY DRS. MICHAEL JACOBSON, WILLIAM LIJINSKY AND ROBERT SCHAFFNER

As members of the Expert Panel on Nitrite and Nitrosamines, we disagree strongly with one of the recommendations of the Panel and are submitting this minority report.

The majority of the Panel recommended that nitrite be allowed in bacon for 3 years, even if that nitrite leads to the formation of nitrosamines in cooked bacon. We believe this recommendation is irresponsible and conflicts with the Federal Meat Inspection Act, which prohibits poisonous and deleterious substances from food. We believe that the use of nitrite should be restricted to those foods in which nitrosamines do not form during processing or cooking. For example, bacon is a food in which nitrosamines sometimes form even when 120 ppm nitrite is used and ascorbate is added.

Dr. Edwards endorses this statement.

STATEMENT BY DR. JAMES P. KEATING

Recommendation 1. There is insufficient information to recommend revision of the present methods of monitoring to include residual nitrite determinations. The recommendation may generate an expensive new activity (supported by tax dollars). I do not believe the public health hazard is sufficient to warrant a large expenditure in this way.

Recommendation 2. I strongly differ with the recommendation that large amounts of ascorbate/isoascorbate should be added to all five categories of cured products since they have been demonstrated to inhibit nitrosamine formation in only one. We have no idea whether they will inhibit nitrosamine formation in products which have not been studied. We have no information concerning what the effect on other aspects of product safety or organoleptic qualities would be.

Recommendation 4. The term "botulism outgrowth" should be struck. Current methods of monitoring involve assessment of toxin production and that term should be used instead of, or in addition to, the "outgrowth" term. Since the first evidence of a botulism problem may well be clinical illness after ingestion of meat products, I would prefer to have the statement indicate that "if there is evidence of botulism toxin production or clinical botulism in individuals ingesting such product, the Department shall take immediate steps. . . ."

Dr. Greenberg endorses the statement concerning Recommendation 2 and Drs. Wasserman and Greenberg endorse the statement concerning Recommendation 4.

STATEMENT BY DR. WILLIAM LIJINSKY

I dissent from the recommendations of the majority of the Panel, formulated at the September 19 meeting, which seems to be an endorsement of current meat processing practices, with no encouragement to improve processing so as to minimize human exposure to carcinogenic N-nitroso compounds.

My recommendations are as follows:

1. Nitrite or nitrate should not be used to process any cured meat in amounts exceeding those necessary to provide desirable taste and color. These levels can be determined and the information is probably available.

2. In no case should more that 60 parts per million of ingoing nitrite be added to the meat. Should this require upgrading of the manufacturing process or improvements in the distribution system to minimize the risk of botulism, these changes must be made.

3. No product should be sold that contains any carcinogenic nitroso compound at levels that are detectable and confirmable by current analytical procedures (approximately 5 parts per billion). This condition includes nitrosamines that are formed during normal preparation of the food for eating.

4. The residual nitrite in meat as it is sold should be monitored and may not exceed 25 parts per million. (This seems to be already achievable by many manufacturers for most products.)

In addition, I find Recommendations 4 and 7 of that report agreeable, provided that in Recommendation 4 the phrase "or increased levels of nitrite" is deleted. I cannot see any justification for allowing levels of nitrite above what we recommend to compensate for poor manufacturing practices.

I think that Recommendation 8 is one which would encourage the meat processors to indulge in yet further delay in implementation of any recommendation for changes in their manufacturing processes. It is not very likely, for reasons that I and others have stated many times, that a connection between the eating of bacon or other cured meat and any particular cancer will ever be found.

As you know, there has been a connection drawn between the eating of meat in general and high incidence of certain types of cancer. Whether from this can be extracted the contribution of cured meats is to me doubtful. Therefore, I think this might be a large expenditure of effort with little return.

My objection to the report as it stands, apart from the levels of ingoing nitrite recommended in Table 1 which I consider much too high, is that it gives further time extension to the meat processors while they accommodate to changes which they should have made 6 or 7 years ago, as soon as the problem with nitrite became apparent. I do not believe that their dilatoriness needs any further public encouragement.

STATEMENT BY DR. AARON E. WASSERMAN

Recommendation 1. It is my belief the "Ingoing sodium nitrite" levels given in Table I should be maximum values. If target values are desired the appropriate mean value should be lower, i.e. for bacon--target level at 100 ppm nitrite ± 20 ppm. An interesting question now arises: If a target level is set the maximum cannot be exceeded, but does that mean values less than the minimum are also illegal? The Panel never discussed setting minimum values that must be attained to provide anti-clostridial activity.

Dr. Schaffner endorses this statement.

Minutes of the Meetings

Minutes of each of the Panel's meetings were assembled and distributed to all who requested them. The minutes as they were orginally issued are presented in this section.

The First Meeting - February 1974

This summary of the first meeting of the Expert Panel on Nitrites and Nitrosamines has been prepared for circulation to interested persons and was reviewed and accepted with modifications at the April 25 meeting of the Panel.

On February 8, the first meeting of the Expert Panel on Nitrites and Nitrosamines convened at 9:30 a.m., Room 218A, Agriculture Administration Building, Washington, DC 20250, Dr. Harry C. Mussman presiding, with opening remarks by Dr. Gilbert Wise. Dr. Wise acknowledged the broad interest in the subject and the desire of the Secretary to receive advice from the Panel that reflects full consideration of all information and data available on nitrites in our food supplies. There were four of the six panel members present, four speakers and 29 other participants and attendees.

Panel members in attendance were Dr. Richard Greenberg, Director of Research, Swift and Company; Dr. James P. Keating, Head of Pediatric-Gastroenterology, University of Washington, St. Louis, Missouri; Dr. Aaron E. Wasserman, Agriculture Research Service, USDA, Philadelphia, Pennyslvania; and Dr. Leo Friedman, Director, Division of Toxicology, Food and Drug Administration, Washington, D.C.

In his charge to the Panel, Dr. Mussman pointed out the need to: (1) establish a suitable foundation of scientific knowledge upon which to base judgments about nitrates and nitrites in foods, and to assure; (2) that the decisions made regarding their use consider the broad base of information that is available; and (3) that all interested persons with opinions and/or relevant information are able to contribute to this broad base of information.

He continued by saying that we must recognize the need to get a better balance between the positive and negative aspects of the questions relative to nitrite, and we must make certain that the public is informed of the reasons when decisions are made. Since there is no such thing as perfect safety, the public must recognize the risks involved.

The first speaker was Dr. Joseph Legg of the Agricultural Research Service speaking on "the occurrence of nitrate and nitrite in soil and water." Nitrate is very common, typically found in plants and is necessary for the synthesis of plant material. He mentioned several important nitrate reviews by the Agricultural Research Service and the

National Academy of Sciences that offer excellent summaries of studies on soil and water nitrates. Many factors influence the level of nitrate in plant materials and in soil. Nitrogen in soils resides in two fractions --inorganic and organic--with 95 percent of nitrogen occurring in the organic complex. Dr. Legg estimated that about 15 percent of applied fertilizer is lost through denitrification by micro-organisms. Animal waste creates large amounts of nitrate and some nitrite in soil, and the sheer volume of animal waste makes it difficult to handle. In a study of Texas well water, it was noted that there was an unusually high level of nitrate caused by a rising water table solubilizing nitrate at a depth of 20 to 25 feet underground. In this instance there was little to be done to correct the problem except to chemically treat the water to remove the nitrate--an action deemed by the speaker to be economically questionable.

Dr. Greenberg asked if the use of the rhizobia micro-organisms associated with legumes would help in decreasing the nitrogen buildup in the soil. According to Dr. Legg, this would result in only a temporary decrease in nitrate as these micro-organisms convert atmospheric nitrogen directly into nitrate in the plant.

Dr. Wasserman asked if the nitrite was a problem in the soil. The reply was no, because organic nitrogen goes to the ammonium radical (NH_4+) to (NO_2) and then almost instaneously to (NO_3). Feed lot areas draining nitrite from animal waste increased the nitrite in the soil to some degree.

Dr. Keating asked if soils with high nitrate could produce vegetables with high nitrate content which, when consumed by infants and children, could result in methomoglobinemia; and if there is any way to locate these areas. Dr. Legg indicated that from surveys the States know the levels of nitrate present in water, and recent surveys now include the study of nitrite as well. The nitrate problem in well water seems to occur in semiarid areas where there is insufficient water to wash away the soil nitrate.

The next speaker, Dr. Jonathan W. White, Chief of Plant Products Laboratory, Agricultural Research Service, USDA, spoke on "the occurrence of nitrate and nitrite in foods." Dr. White confined his discussion primarily to fruits and vegetables. The nitrate content of fruits is extremely low; however, vegetables are often significant sources of nitrate with levels greater than those found in cured meats. Vegetables, such as spinach, beets, celery, collard, endive, kale, mustard greens, radishes, and turnip greens are strongly affected by species, variety, plant part, stage of maturity, and environmental factors. These vegetables have high levels of nitrate that often vary from 800 to 4,000 parts per million (ppm) on a fresh basis. On the other hand, beets, carrots, potatoes, and similar vegetables have a very low content of nitrate. Studies on nitrate and nitrite content of spinach leaves indicate that wide varietal effects exist, although the levels of

nitrate may reach 3,000 ppm when grown in soil with 250 milligrams of nitrate per kilogram of soil. However, the nitrite content of spinach was from 1.65 to 2.2 ppm when grown in soil with this nitrate level. Thus, even though nitrate levels are high, the nitrite levels are very low. Factors that affect nitrate content include practices such as the over-fertilization of lettuce just prior to harvest to keep it in excellent shape. Effective weed control chemicals affect crops differently. In some crops, these chemicals will increase the nitrate content of crops; however, they decrease the nitrate content of wheat. Plant genetics exercise a certain degree of control over the nitrate content of crops, but it probably will affect protein content of finished product also. If nitrate is reduced in the soil, crop yields are adversely affected. Dr. White pointed to several cases of home-prepared spinach puree, stored up to 3 days, that resulted in methemoglobinemia in infants in Germany. Another case of this condition resulted from canned beets used as infant food. An ARS study on white potatoes showed no noticeable problem with nitrate or nitrite with varietal effects from 51 to 87 ppm of nitrate.

When questioned about the possible nitrosamine formation in abused, stored beets and spinach, Dr. White said there were no nitrosamines detected by mass spectrophotometry. Shredded spinach which had 2,000 to 4,000 ppm nitrate had no detectable nitrosamines; however, nitrites have been found in spinach that was frozen, thawed, and refrozen several times.

Dr. Keating recalled a study of nitrate in carrots produced in the western United States compared with "organically grown" carrots purchased at organic food stores-the latter product had higher levels of nitrate. Dr. Keating asked about the abused spinach. It appeared from the data that after 10 days of abuse, spinach reached a level of 1,200 ppm of nitrite. Dr. Wasserman commented that although the nitrite was high, the pH was high, and thus there would be no nitrosamine produced.

The next speaker was Mr. Richard Ronk, Food and Drug Administration (FDA), who spoke on "food additives and their control." He defined the food additive established by the food additive amendment of 1958 as a substance the use of which either directly or indirectly would become a component of a food. He pointed out that a food additive would be anything except:

1. food,

2. compound with no prior sanction,

3. compound that is generally recognized as safe by experts qualified to make such determination (e.g. a food safety scientist),

4. pesticide,

5. color additive,

6. animal drugs except as animal drug residues, are of significant quantity in finished foods,

7. reasonable level of a substance normally present in that food.

Packaging has been given much attention by the Food and Drug Administration since most of the food additives are cleared in relation to packaging materials. Food additives are toxic substances, but if FDA recognizes that these have value they will determine at what level of use they are not necessarily hazardous. Hazardous substances such as food additives must be controlled by regulation. Functionally, there are 10,000 regulated food additives; there are approximately 675 "generally-recognized-as-safe" (GRAS) compounds, but 478 of these are nonflavor substances.

As for prior sanctioned items, such status was established in the past by letters from FDA to individuals stating that, in FDA's opinion, the substance was safe. If the substance is later found unsafe, then it would require a food additive regulation for continued use. Mr. Ronk stated that there are presently 40 colors approved by FDA. Since 1970, GRAS affirmation has been sought on a number of compounds that heretofore have not been recognized--it appears that there will be about 2,800 compounds (mostly flavoring compounds). Nitrate and nitrite are sanctioned by USDA prior to commercial curing of meat and poultry products under inspection, and controlled by FDA regulation for curing fish and home curing of meats.

Mr. Ronk next discussed the requirements for a food additive petition: (1) the petition must prove that the compound is safe; (2) the additive must accomplish the task intended; (3) the additive must not be deceptive in any way; (4) the additive must have a reasonable method of control; and (5) information used to support the safety and use of the additive cannot be proprietary--and all information must be in the public domain.

Dr. Wasserman asked Mr. Ronk that if only manufacturers petitioned for additive approval, what happens if there is no petition? The Commissioner, according to Mr. Ronk, may decide according to law to regulate the substance rather than to declare it as GRAS. The Commissioner would publish an order with 30 days for comments from adversely affected individuals.

Dr. Keating asked what was the purpose for approval of nitrate and nitrite? Mr. Ronk replied that it was used as a color fixative, and it was later learned to be a preservative-a bacteriostat.

Dr. Mussman pointed out that there is a USDA regulation limiting the use of nitrite by setting maximum permissible levels in the finished cured product. Dr. Mussman noted that USDA applied the same rules as FDA in granting approval of a substance as an additive in federally inspected meat and poultry products.

Mr. Ronk believes that there will be only a few new additives developed each year--(4 or 5), however, there will be a large number of additional functional effects approved for presently approved additives.

Dr. Mussman recapped the morning session by saying that the presentations on nitrite and nitrate in the soil, water and food had given some insight as to the ubiquitous nature of nitrates and nitrites and how these are controlled as additives. These facts help to give a better understanding of the quantity of nitrate and nitrite present in food and gives a better balance and broader base upon which to make judgments about the propriety of use of these substances.

The afternoon session was attended by five panel members, four speakers and 27 other participantes and attendees. Dr. Cecile H. Edwards, Head of Home Economics, Howard University, Washington, D.C., was introduced as a member of the Panel.

Dr. Robert Cassens of the Muscle Biology Laboratory, University of Wisconsin, presented the final talk entitled "The Curing Process." He pointed out that cured hams differ from fresh hams in that they have a difference in color, a slight difference in texture and remarkable difference in taste from that of a cooked fresh ham. Dr. Cassens traced the history of the curing process back to before the time of Christ. Significant research work by Haldane in 1899 indicated that the pigment of cured meat was nitric oxide hemochromagen, and further that nitrite is destroyed during prolonged cooking of meat products cured with nitrates. The USDA work of 1925 was the basis for the regulation that limited the amount of nitrite and residual product nitrite to not more than 200 ppm. This work led to the introduction of nitrite as a curing ingredient in lieu of nitrate--nitrite had been found to be the active curing ingredient while nitrate serves only as a reservoir for nitrite.

Dr. Cassens briefly reviewed the methods of curing, the curing ingredients, their functions, and pointed out that nitrite has four distinct functions: (1) development of the natural cure color; (2) development of a characteristic cured meat flavor; (3) inhibition of micro-organisms; and (4) inhibition of rancidity. He also reviewed the various oxidation states of myoglobin.

Dr. Cassens discussed the difference in quantity of red muscle fibers (high myoglobin content) and white muscle fibers by species--the rabbit had a high content of red fibers, the pig a slight amount, and beef a modest amount of red fibers. He suggested that the Panel may wish to consider these two points: (1) Aside from the well-known effects of species and age on myoglobin content of muscle, there is, at the microscopic level, a differential concentration of myoglobin in the individual fibers known commonly as the red and white types; and (2) there are several layers of connective tissue which are intimately associated with the cell wall of the muscle fiber. Curing ingredients must therefore

pass over or through an extensive bed of connective tissue before they arrive at the pigment, and they would have good opportunity to interact with such components before reaching the pigment.

Studies at Wisconsin using N_{15} labeled nitrite franks stored for 70 days showed that residual nitrite decreased markedly while the labeled N_{15} compound increased in the components of muscle. The nitrogen in residual nitrite becomes dispersed throughout many different compounds present in the tissue. Theoretically, 10 percent of added nitrite is required to combine with the pigment on a mole-for-mole basis. If another 30 percent remains as residual nitrite, then 60 percent of the added nitrite remains unaccounted for-it has disappeared.

As for substitutes for nitrites, these would be either of the pyridine class which are less stable as color pigments or vegetable dyes. The latter have the problem of being water soluble and leaching from the meat into water. Dr. Cassens mentioned in closing that the trend in industry has been toward reduced use of nitrate in curing formulations--particularly with accelerated curing in the last 25 years. There has also been an increased use of ascorbates and related compounds during the past 20 years. The effect of ascorbates is two-fold: they accelerate the curing process and stabilize the finished cured color.

In summarizing, he said that curing is accomplished by adding salt, possibly sugar, and nitrate or nitrite to meat. The essential ingredient is nitrite which when reduced to nitric oxide combines with myoglobin. Heat denatures the protein portion resulting in a stable pigment which has a distinctive pink color. Nitrite also results in the characteristic flavor and texture. Lastly, nitrite provides specific protection against the outgrowth of spores of Clostridium botulinum.

In response to questions, Dr. Cassens said that there is no substitute for nitrite for flavoring purposes. Dr. Friedman asked about the fractions of meat that combine with the labeled nitrite. Dr. Cassens stated that about 10 percent of the N_{k5} was pigment-associated, 10 percent was in gaseous nitric oxide(difficult to trap), 2 percent was in head space, a large portion was in the water soluble compounds (low molecular weight materials), 10 percent or less was in the salt soluble compounds (such as myofibrillar proteins) and 15 percent was associated with the residue or the connective tissue.

Dr. Edwards was concerned whether one could inhibit Clostridium botulinum by other means. Could Americans adapt to the different color and flavors of meat produced without nitrite? Dr. Cassens believed this would be very difficult. Dr. Edwards agreed.

Dr. Friedman asked about the role of ascorbates in the curing process. Dr. Cassens replied that it: (1) increases the yield of NO from NO_2; (2) speeds up metmyoglobin reduction; and (3) maintains color stability due to its reducing power.

Dr. Keating asked why there has been a reduction in nitrate use? Dr. Cassens replied that nitrite is the active ingredient. He did not know of other effects of nitrate beyond that of supplying nitrite.

Dr. Friedman wondered where nitrate is playing a role. In dry-curing processes, according to Dr. Cassens, nitrate serves as a reservoir for nitrite and in the making of fermented sausages, it may play a similar role.

Dr. Wasserman asked if there are no-nitrate and no-nitrite franks in health food stores? Dr. Cassesns replied that there are some white sausages (e.g., cooked knockwurst and weisswurst) which do not contain cures and also there are products to which they have added beet powder as a colorant.

Dr. Wasserman asked if one could safely store the no-nitrite franks? Dr. Cassens replied there may be a danger.

Dr. Mussman asked how widely nitrite and nitrate are used worldwide? Dr. Cassens replied that they are widely used. Some exceptions exist in that no-nitrite sausages have been prepared both domestically and abroad where they are well-handled with no botulinal problems. There has been no botulinal problem with a Norwegian product consisting of a salted, dry, mutton leg. However, in Paris ham (a cooked ham with no nitrite), there are occassional botulinal deaths. In Scandinavia, there is a no-nitrite liver paste which is baked but not refrigerated--it is also a very definite botulinal hazard. The safety of knockwurst depends on the care which the product receives. Most people consuming it know that it must be handled very rapidly and eaten within a week. Dr. Cassens did not know the salt content of the Norwegian mutton but assumed that it would be rather high.

Dr. Edwards wondered if vitamin E could be used as an antioxidant. Dr. Cassens did not know.

Dr. Greenburg stated that in their study of fermented sausages nitrate was not needed for botulinum protection, but they did need fermentable sugars and nitrite. He agreed that the country-style ham is the only product that perhaps needs nitrate in the cure and further stated that vitamin E seems to prevent rancidity but product has a different flavor.

Mr. Ronk commented that with good manufacturing practices plus sufficient cooking, nitrite is unnecessary in smoked fish if the product is refrigerated.

Dr. Edwards asked Dr. White if there was a nitrite source from foods other than meats? Dr. White replied that if vegetables are not abused there are no significant amounts of nitrite. (The highest level was about 2 ppm.)

Dr. Wasserman, commenting on the matter of nitrite in human saliva, indicated that after eating foods high in nitrate, there was an increase in the nitrite content of saliva. Dr. Greenberg commented on Dr. Steve Tannenbaum's work at MIT in which he found that 10 to 12 milligrams per day was the total outpoint of nitrite in human saliva, but it was highly variable. The salivary gland contains nitrate but no nitrite; thus bacteria in the mouth are presumed to be converting nitrate to nitrite.

Dr. Edwards asked whether irradiation coupled with low levels of nitrite would control micro-organisms; and if irradiation would result in higher levels of nitrite in finished products. Dr. Greenberg said no to the latter question. Mr. Ronk commented that irradiation must have a food additive regulation, and at the present time, there is extensive research being done by the Army Natick Laboratories in pursuit of possible clearance of irradiation for foods.

Dr. Mussman asking Dr. Cassens about data that had been generated by industry in support of the use of nitrite said, "Is it your impression that this level of nitrite is justified?" Dr. Cassens replied that the work on nitrite with canned hams, frankfurters, and bacon seems to verify the need for near the amount now permitted by regulation.

Dr. Mussman asked Dr. Cassens whether the meats now produced, such as canned products, were a botulinal hazard. He replied that if botulinum spores were present, if there were no nitrite used and if the product were not refrigerated, there was a definite possibility of a botulinal hazard.

Dr. Friedman asked about chances that the food would spoil and be unacceptable so that a person would reject the product that might contain botulinal toxin. Dr. Cassens replied that the product may appear to be acceptable but still have toxin.

Dr. Greenberg asked about freezing all luncheon meats and similar products produced without nitrite. Dr. Cassens replied, this would not be good because of off flavor due to rancidity as a result of there being no protection from rancidity by nitrite.

Dr. Greenberg recapped the American Meat Institute studies completed by industry and the reasons why industry had agreed to do these studies in cooperation with both FDA and USDA. Dr. Greenberg displayed a table showing levels of nitrite added to product by different product types (ham, franks, bacon, and thuringer) and gave the percentage of product which had botulinal toxin present.

PERCENT OF SAMPLES SHOWING BOTULINAL TOXIN

Product	Spores introduced (per gram)	Nitrite Added (ppm) 0	50	100	150	200	300
Ham	90	56	40	20	2	0	0
Franks	620	58	1	0	0	0	0
Bacon	210	95	60	36	19	6	0
Thuringer	1500	0	20	0	-	-	-

Dr. Greenberg concluded by saying that products vary considerably in their need for nitrite. Franks and thuringer require a small amount of nitrite while bacon and hams require rather high levels of nitrite.

Dr. Mussman asked Dr. Greenberg what amount of residual nitrite remains in product that goes to the consumer. Dr. Greenberg replied that two-thirds of the nitrite is destroyed during processing and cooking of bacon and that one-half of the nitrite is destroyed in ham and franks. If in three meals one consumes 3 ounces of bacon for breakfast, 3 ounces of franks for lunch and 3 ounces of ham for dinner, 12 mg of nitrite is consumed per day. Coincidentally, this corresponds with Dr. Tannenbaum's estimate of 12 milligrams of nitrite per day present in saliva.

Mr. Ronk commented that the quantity of nitrite used in meat curing is not permitted to exceed that amount that is reasonably required to perform the purpose intended. Dr. Mussman stated that this was the USDA requirement also. Mr. Ronk and Dr. Friedman agreed that over-irradiated meats have a very poor flavor and problems of oxidation. Dr. Edwards pointed to the need to know more about the effects of nitrite on other parts of the human body.

At this point, Dr. Mussman invited questions from the floor. Dr. Michael Jacobson of the Center for Science in the Public Interest pointed out that this meeting was a long time in coming, about 2 years. He then questioned the size of the botulinum problem. He asked, "How many spores are normal to product, how many deaths do we have from botulinum?" Dr. Mussman explained that microbiology would be explored at a later session of this Expert Panel. Dr. Wasserman added that in Europe 6 to 12 botulinum deaths occur per year from meats. Mr. Ronk pointed to the problem of recontamination of product after nitrite administration. To this, Dr. Greenberg also added information about numbers of botulinum spores. In a 1967 study, one of 73 luncheon meat samples had type-B C. botulinum; one of 10 franks in a 1969 study contained type-B C. botulinum, and in a 1971 study in California on sliced, cooked ham 5 of 100 had type-A C. botulinum spores. Mr. Ronk pointed out that in crab meat, 10 of 400 had C. botulinum spores after the crab meat was

processed. Dr. Freidman pointed out that Clostridium botulinum is a soil micro-organism that is ubiquitous and that not all spores are associated with toxin.

Ms. Fitzgerald of the Center of the Study of Responsive Law asked if there were any bacon samples with botulinal spores? Dr. Greenberg said, "No."

Ms. Fitzgerald then asked about the quantity of nitrosamines in product. Dr. Mussman replied that in late 1971 and early 1972, the program reported three positives in meat products. Now with 100 assays completed, they have found no additional positives. Dr. Friedman summarized research over 3 or 4 years by saying that nitrosamines in meat have been very low and with no set pattern. He continued by citing recent changes in curing mixtures that prohibits nitrite in intimate contact with spices, such as pepper. This mixing has been shown to possibly contribute to nitrosamines found in frankfurter samples.

Ms. Kugler of Food Chemical News asked whether hotdogs with no nirite or nitrate present any problems? Dr. Wasserman said that when kept frozen after 1 week, franks have a loss in flavor.

Dr. Jacobson commented that he found no-nitrate, no-nitrite frankfurters quite acceptable for consumption. Dr. Friedman and Mr. Ronk commented on the approval for nitrite use for color and flavor but noted that only recently had nitrite been found to be functional as a preservative.

Mr. Ronk commented that FDA's proposal limiting the use of nitrite has met with very little response. Dr. Jacobsen asked what has happend to the Norway nitrite-nitrate proposal. Mr. Ronk said they did not know, but he would find out.

Dr. Jacobson asked if USDA and others had done any work on alternative curing methods. Dr. Cassens replied that high salt content and high temperature cooking would control botulinum, but this produces an objectionable product; the product has been changed and becomes rancid rapidly.

Ms. Fitzerald asked how much research effort has been directed toward nitrite and nitrosamines over the last 3 years. Dr. Wasserman said that they have increased their staff considerably. Mr. Ronk stated that 4 years ago in FDA there were 3 professional man-years dedicated to the nitrite and nitrosamine question, now there are 15. FDA now has a $384,000 contract at MIT on the toxicological aspects of nitrosamines.

Dr. Jacobson asked that the USDA consider labeling bacon "caution, may be injurious to your health." Mr. Ronk commented that such labels would probably be misleading. Dr. Jacobson asked whether the Delaney amendment to the Food, Drug and Cosmetic Act would affect nitrite?

Mr. Ronk replied that since nitrite is prior sanctioned, it is not subject to the Delaney amendment.

Dr. Mulhern, the Administrator of APHIS, commented on the great importance of this Expert Panel and noted that although it might have seemed to be slow in forming, that this Panel is now receiving information and should carefully weigh all the facts and make their own judgments in developing recommendations to the Secretary.

The afternoon session of the Expert Panel was closed by Dr. Mussman as he briefly summarized the important points of the meeting and stressed the importance of basing final decisions upon facts as they are brought to light for the Expert Panel. The meeting concluded at approximately 4 p.m.

The Second Meeting - April 1974

The second meeting of the Secretary's Expert Panel on Nitrite and Nitrosamines convened at 9 a.m. in Room 218 of the Agriculture Administration Building, 12th and Independence Avenue, Washington, DC 20250.

Dr. Harry C. Mussman, Executive Secretary to the Panel, opened the proceedings with a statement on the general purpose of the Panel, its areas of consideration, and a brief review of the Panel's first meeting held on February 8, 1974. There were 31 persons in attendance, in addi-tion to five Panel members and four speakers. The Panel members present were: Drs. Leo Friedman, Richard Greenberg, James P. Keating, A. E. Wasserman, and John H. Weisburger. Dr. Weisburger, who was unable to attend the first Panel meeting, is Vice President for Research, Naylor Dana Institute for Disease Prevention, New York City. Dr. Cecile H. Edwards, a Panel member, was not present.

Dr. Mussman asked for corrections and/or comments to the summary on the February 8, 1974, meeting of the Panel. There were no comments from the group; however, several Panel members, in correspondence, had suggested minor changes which had been incorporated. The Panel approved the summary with those corrections.

The first speaker was Dr. Walter Fiddler of the Eastern Regional Research Center, ARS-USDA, Philadelphia, Pennsylvania, who has been largely responsible for chemical studies on nitrites and nitrosamines conducted at the USDA eastern regional research facility. He explained and illustrated the chemical reactions that take place and result in formation of nitrosamines through the combination of nitrite and secondary or tertiary amines. His work, he indicated, has shown that several factors affect nitrosamine formation: (1) formation of N_2O_3, the actual nitrosating compound, is dependent on the square of the NO_2 concentration; (2) basicity (degree of alkalinity) of the amine affects the rate of reaction; and (3) time and temperature affect the magnitude of reaction. Dr. Fiddler concentrated his presentation on the amino acid precursors of nitrosamines with the strong suggestion that proline may be an important precursor as it is present in abundance in the connective tissues of meat.

In the second part of his presentation, Dr. Fiddler discussed methods of sample preparation and analytical procedures.

In response to questions by the Panel, Dr. Fiddler: (1) listed foods in which nitrosamines have been reported; (2) labeled as erroneous a report of nitrosamines in alcoholic beverages; (3) said a false peak that was detected during nitrosamine analysis most likely was a result of a silicon compound used in the gas chromatography (GLC) column; (4) explained

the new plasma chromatograph; (5) said that there were shortcut methods to screen for nitrosamines; and (6) stated that the levels of sensitivity were 0.5 ppb for GLC, and 2 ppb for mass spectrometer.

The next speaker was Dr. Ronald Shank, Nutrition and Food Science Department, MIT, Cambridge, Massachusetts, who addressed the subject "Toxicology of N-Nitroso Compound." He indicated that the sites of cancer formation associated with nitrosamines are extremely varied and that toxic doses of nitros-amines also vary depending upon the specific nitrosamine. Lethal doses as reported in the literature range from 18 mg/kg body weight to 7500 mg/kg body weight. Dr. Shank concluded by saying that no one specific alkylated base can be considered critical in carcinogenesis. As yet, it is not clear what role alkylation of nucleic acids and other macromolecules plays in cancer induction, but the large number of N-nitroso compounds presently being studied and the number of tissues which exibit carcinomatous responses will prove powerful tools in the study of chemical carcinogenesis.

In response to questions, Dr. Shank: (1) acknowledged that there is no apparent relationship between acute toxicity and carcinogenesis; (2) stated that not all nitrosamines are carcinogenic; (3) said that carcinogens move about and will cause cancer wherever they are metabolized; (4) stated that there is very little work on mutagenesis or teratogenesis; and (5) indicated that dimethylnitrosamine was mutagenic at high levels and seems to function similarily also at low levels.

Dr. Charles Duncan, Food Research Institute, Madison, Wisconsin, presented a paper on the interaction between nitrite and clostridia. He briefly covered the ancient origins of the use of nitrate as a salt impurity in meat preservation and developed the idea that meats prepared without nitrates a/o nitrites can be lethal if the food is mishandled. He next explained the mode of action of nitrite on the bacterial spore indicating the various factors that would affect spore growth and pointed out that the heat resistance of the spore can be altered by a change in its ionic composition as the spore is influenced by previous environment. Because of this situation, it is difficult to predict the exact level of nitrite needed to inactivate the botulinum spore.

In response to questions, Dr. Duncan: (1) stated he has been unable to demonstrate the socalled "Perigo effect;" (2) indicated that highly perishable meat products prepared without nitrite are customarily handled carefully by the user and remain safe (frozen in distribution); (3) declared that it is difficult to state the minimum of nitrite needed for protection--the levels presently permitted are sufficiently high, but conditions vary for each product and no clear answer is apparent; (4) was not positive how many spores are normal to meat; and (5) believes that enzymic treatment is impractical as a means of sensitizing the botulinum spore to enhance the effectiveness of nitrite.

After an ajournment for lunch, Dr. Mussman reconvened the meeting by introducing Dr. William Lijinsky, Carcinogenesis Program, Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830, who spoke on the subject "A View of the Problems Associated with Nitrite Usage." Nitrite is regarded as highly toxic to animal life, Dr. Lijinsky indicated, with the degree of toxicity directly proportional to the amount ingested at any one time. To illustrate, he stated that even though rats are killed by single doses of 400 mg/kg body weight, those given repeated lower doses (100 mg/kg body weight) appear to suffer no ill effects. Rats continously fed 40 mg of nitrite per day for 2 to 3 years live in seemingly good health. Dimethylnitrosamine (DMNA) on the other hand is a potent carcinogen and appears to induce tumors in almost all organs of the rat. When rats were fed aminopyrine plus nitrite for 50 weeks at a level of 250 ppm in drinking water, 14 of 15 males and 13 of 15 females developed liver tumors. Dr. Lijinsky pointed out that secondary amines (e.g., aminopyrine) combine with nitrite to form nitrosamines under proper conditions of pH and even teritary amines will form nitrosamines at a pH greater than 3. Dr. Lijinsky cited his research using common drugs of the tertiary amine type often prescribed for humans. He found that, under the proper conditions, most of them will produce nitrosamines when reacted with 0.04 percent sodium nitrite.

Dr. Lijinsky, during his discussion, frequently called for a reduction in the residual nitrite in cured meat. He did not deny, however, the need for adequate nitrite to protect the product from C. botulinum.

Dr. Greenberg, responding to a query by Dr. Lijinsky, briefly reviewed the history of Dr. Jensen's theory supporting the use of nitrite in cured meats. When asked by the Panel, Dr. Lijinsky indicated he: (1) believes that the currently permitted residual nitrite level of 200 ppm is too high and is arbitrary; (2) fears that even 20 ppm of nitrite will react with aminopyrine to form nitrosamines; (3) thinks that two-thirds of the theoretical yield of nitrosamines will be possible in 1 hour in the stomach if proper reactants are present; and (4) believes that gastric cancer in man is not a significant concern.

The meeting continued with a general discussion between the Panel members and the agenda speakers that centered around the development of cancer in man and test animals. The possibility of using increased amounts of ascorbate to reduce the residual nitrite was discussed. Dr. Lijinsky was in agreement with such use but cautioned that larger amounts of ascorbates should not be an alternative to reducing the residual nitrite where possible. Recent research from the Food Research Institute was cited as showing that as the level of ascorbate increased the botulinal protection by nitrite was reduced.

Dr. Mussman indicated that the Panel is reaching a point where it should consider making one or more recommendations and suggested it would be appropriate to circulate some nitrite data to the Panel before the next

meeting. The Panel agreed. The meeting concluded with mention by Dr. Mussman that the next meeting, June 19, would include a review of the cooperative study by AMI, FDA, and USDA on the microbiological and chemical aspects of nitrite, nitrates, and nitrosamines in various product categories. The meeting ajourned about 4 p.m.

The Third Meeting - June 1974

The third meeting of the Secretary's Expert Panel on Nitrite and Nitrosamines was convened at 9:10 a.m., June 19, 1974, in Room 218A of the Agricultural Administration Building, 14th Street and Independence Avenue, Washington, DC 20250. There were 44 persons in attendance, in addition to the six Panel members and four speakers.

Dr. Harry C. Mussman, Executive Secretary, opened the meeting with introductory remarks about the Panel meetings held February 8 and April 25, and directed the Panel's attention to a letter from Merek and Company and to a summary of USDA data on residual nitrite in cured meat products. Dr. Mussman asked if there were corrections or additions to the summary of the April 25 meeting of the Panel. There we no corrections and the summary was accepted as written.

The first speaker was Mr. Evan Binkerd, Vice President and Director of Research for Armour and Company, Oakbrook, Illinois, who reviewed the history of nitrate and nitrite use in meat curing. He stated that these curing agents were originally present as incidental contaminants of salt and that salt curing was practiced as early as 3000 BC in Mesopotamia. He traced the history of curing practices and the writings of practitioners and scientists up to 1925 when the Bureau of Animal Industries, USDA, issued BAI Order 211 (revised) that provided for the use of sodium nitrite in chopped meat in amounts not exceeding 1/4 ounce per hundred pounds of meat and established a limit of 2 pounds nitrite per 100 gallons of pickle solution or 1 ounce to 100 pounds of meat in dry cure. Binkerd noted that the curing of meat cuts in a pickle solution only was generally practiced up to about 40 years ago when stitch pumping and artery pumping became available procedures and led to combinations of pumping and submerging in pickle cure. Today, these combination procedures are declining in importance with emphasis being placed on rapid processing. He presented tables showing residual nitrite and nitrate by product type reported in the late 1930's and in 1971 and 1972. A survey of the major U.S. packers in 1970 and 1974 showed a marked decrease in use of nitrate (many packers no longer use nitrate) and a slight increase in level of nitrite to assure adequate protection from C. botulinum.

In response to questions, Binkerd: (1) agreed that the increase in nitrite use was a result of recent botulinal studies; (2) explained the term overhauling in relation to cured products as a replenishment to the cure materials.

Dr. Mussman discussed with the panel a summary of 1970-71 USDA laboratory data on residual nitrites from 6,537 analyses. He emphasized that 98.4 percent of the samples contained no more than 100 ppm of residual nitrite and that 92.7 percent contained no more than 50 ppm. Mussman

also called attention to a letter from Dr. Jonathan White, ARS, a speaker at the first panel meeting, in which White estimates that the daily nitrite intake is 11.6 mg. of which cured meats contribute 5 mg.

John Bard, Vice President for Research, Oscar Mayer and Company, Madison, Wisconsin, summarized results of joint studies by the American Meat Institute, FDA, and USDA, on the following four types of processed meats: perishable canned comminuted cured meats, cooked sausage, bacon, and fermented sausage. This combined research effort was designed to answer three questions: (1) does nitrite at present levels reduce risk of C. botulinum toxin formation; (2) are detectable levels of nitrosamines formed when presently permitted nitrite levels are used; (3) can changes in permitted curing agents be made that would reduce risk of nitrosamine formation? The studies showed that: (1) nitrite needed is dependent upon bacterial inoculum level; (2) nitrite is effective in preventing formation of botulinal toxin; (3) nitrate is essentially nonfunctional as a botulinal inhibitor; (4) residual nitrite decreases rapidly during meat processing and continues to decrease with time; (5) the quantity of nitrite needed for botulinal protection also varies by product type.

At levels of nitrite presently permitted, no nitrosamines were found in any product except fried bacon. With bacon, the cooking method affected nitrosopyrrolidine formation; pan-fried bacon had greater amounts of this nitrosamine than oven-cooked or microwave-cooked bacon. Ascorbate at higher levels seemed to reduce or inhibit nitrosamine formation in bacon, but later studies showed that ascorbate also reduced the effectiveness of nitrite as a botulinal protector. Bard further reported that no samples containing botulinal toxin were noted in the fermented sausage study and such sausage with 50 ppm nitrite would produce toxin only if either dextrose or sugar was not present to bring about the fermentation and lowering of pH.

Dr. Jay Fox, Meat Scientist, Eastern Regional Research Center, ARS, Philadelphia, Pennsylvania, explained: (1) the role of ascorbate in cures; (2) reduction of nitrite by ascorbate; (3) inhibition of nitrosamines by ascorbate; and (4) reversal of nitrite inhibition of C. botulinum growth. He pointed out the extremely complex chemical nature of meat and showed that the quantity of endogenous reductants is 12 to 40 times that contributed by ascorbate. Fox stated that 97 percent of the ascorbate is lost in 4 hours, that 1/3 is lost immediately upon addition of nitrite, and that nitrite is constantly being regenerated in minute amounts during processing and storage.

In response to questions, Dr. Fox said: (1) substantially higher levels of ascorbate could be used, but this could overload the system and cause salting out of ascorbates; (2) there was no upper limit of ascorbate for color formation, but it must reach a balance with other chemical constituents; (3) a two-step process of cure and then ascorbate would not be

effective in many products as meat becomes quite refractory after cooking; and that (4) cysteine present in meat is almost as effective a reducing agent as ascorbate.

The final discussion was presented by Dr. Hardin B. Jones, Professor of Medical Physics and Physiology and Assistant Director of Donner Laboratory, University of California, Berkeley, California. In his talk, entitled "Estimation of Environmental Factors in the Origin of Cancer and the Hazard of Carcinogenesis in Regard to Nitrosamines," Dr. Jones explained his theory that the cube root of the dose predicts the latent period of carcinogenesis. Data on onset of leukemia among survivors of the atomic bombing of Japan and data on diethylnitrosamine, dibenzanthracene, and other carcinogens were used by Jones to develop this theory. The dose-effect relationships were linear and the time relationship was such that alteration of the dose by one thousandfold usually caused a tenfold change in the time of tumor induction. Based on rat and mouse data and assuming a 30 times greater lifespan for man in comparison to rats and mice, Jones estimated that the risk of cancer from possible nitrosamines in cured meats is about 100 times the life span of man. Dr. Jones concluded by saying that urethan is the only carcinogen discovered that does not conform to the inverse cube root principle.

Dr. Jones responded to questions by: (1) agreeing that there is also a threshold for stilbestrols; (2) proposing that new information now allows the design of studies to gain toxicological information; (3) stating that he believes research will also find a threshold for irradiation; and (4) noting that co-carcinogenesis study results are scattered and random, thus necessitating a repeat of many experiments to study multiple etiology carcinogenesis.

Dr. Mussman next invited Panel members to direct questions to the speakers. Dr. Fox believes there is a middle ground level of ascorbate, but it must be determined on a product-by-product basis. Dr. Weisberger asked if benzoate could be used for microbial protection, but no one could reply. Mr. Binkerd said that a ban on the use of cures with meats would create havoc in the agricultural industry, especially the pork industry as 60 to 70 percent of all pork is cured. All speakers agreed that the 200 ppm of residual nitrite is archaic, as much product contains less than 50 ppm residual nitrite. It was also agreed that control of residual nitrite at the retail store level was not practical.

At 3:25 p.m., comments were invited from the audience. Dr. Eugen Wierbicki, Natick Army Laboratories, discussed use of ionizing irradiation and cures at low levels. He recently noted that deletion of sugar from the cure appears to reduce residual nitrite in ham and bacon. Dr. Leon Rubin, Director of Research, Canada Packers Limited, commented on forthcoming Candian regulations which will permit 200 ppm nitrite to be added to solid cuts of meat except bacon--bacon and sausage products would be permitted 150 ppm.

Dr. Mussman concluded the Panel meeting by saying that there were several alternatives for the Panel to consider: (1) reduce residual nitrite; (2) reduce initial nitrite; (3) eliminate nitrate by product class; and (4) establish levels of ascorbate that would assist in control of nitrite residual. Dr. Weisburger also suggested that the Panel consider supplementing nitrite with benzoate.

Dr. Mussman set July 15 as the date for the next panel meeting. The meeting was adjourned at 4 p.m.

The Fourth Meeting - 1974

The fourth meeting of the Secretary's Expert Panel on Nitrite and Nitrosamines was convened at 9:38 a.m., July 15, 1974, in Room 509 A of the Agricultural Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250. There were 40 persons and five panel members in attendance.

Dr. Harry C. Mussman, Executive Secretary, opened the meeting and announced the loss of a most valuable Panel member, Dr. Leo Friedman. A moment of silence in memoriam was observed.

Dr. Mussman briefly reviewed the history of benzoate usage as a preservative for meat products before 1948. The Department of Agriculture withdrew permission for use that year because it was shown to contribute little microbiologically in most products in which it was employed.

In a letter written just a few days before his death, Dr. Friedman suggested that there were five main points at issue which the Panel should keep in mind. Dr. Mussman indicated that they accurately reflected the specific areas to be considered and stated they could serve as a basis for Panel deliberations. The points Dr. Friedman raised were:

1. Is there any basis to continue the use of nitrate in any specific product?

2. Is there a basis for changing, in general, or for any specific product, the initial nitrite levels?

3. To what level can we reduce the tolerance for residual nitrite, either in general or in each specific product category?

4. Is there sufficient basis to require the mandatory use of ascorbic (acid) in the nitrite cure, and what is the optimum level, in general, or for each specific product, to accomplish the greatest enhancement of the botulinum outgrowth inhibition, and the greatest reduction of residual nitrite?

5. Is there any product category where nitrite is now permitted where the nitrite cure should be forbidden?

The Panel discussed these questions on a product category basis as follows: (1) cooked sausage (e.g., franks, polish sausage), (2) bacon, (3) canned cured perishable or shelf-stable product (e.g., canned ham, canned chopped meat, canned corned beef), (4) fermented sausage (e.g., salami, pepperoni, Genoa salami, summer sausage, cervelat), (5) pickle-cured primal cuts except bacon (e.g., ham, Canadian bacon, corned beef),

(6) canned cured sterile product (deviled ham), (dry-cured primal cuts (e.g., country ham, dry-cured bacon).

With regard to the first point mentioned, the Panel agreed that nitrate has neither organoleptic nor public health functions in cooked sausage, bacon, canned cured perishable and shelf-stable product, pickle-cured primal cuts, and canned cured sterile product. Dr. Greenberg made the point that this concept referred only to those products as produced in the United States and Canada. There is a definite utility for nitrate in many cured meat products in other nations. In addition, there is some question regarding the requirement for nitrate for organoleptic purposes in a few fermented sausage products manufactured in the United States and Canada. As the discussion moved to dry-cured products and the question of nitrate, Dr. T. N. Blumer, North Carolina State University, described the dry cure process in detail and concluded by saying that typically, dry-cured hams contain levels of residual nitrite that vary between 0 and 10 ppm. Robert Dudley, Director of Research, George Hormel Company, discussed a single very limited experiment at Hormel which suggested that dry-cured product could be manufactured without nitrate, thus utilizing a straight nitrite cure.

Dr. Mussman recommended that the Panel either propose to remove nitrate from all products, or from all products except fermented sausage and dry-cured products. In response to these suggestions, the Panel recommended that nitrate be eliminated from all cured products except fermented sausage and dry-cured products (e.g., salami, pepperoni, country ham, and dry-cured bacon). The Panel subsequently urged that studies be encouraged to determine the need for nitrate in these two categories of product and Dr. Weisburger asked that 2 years be allowed for their completion to assess the need for nitrate for either technologic or organoleptic function. Concern for small processors not accustomed to using nitrite was expressed by Dr. Blumenthal, FDA, who believed that because of processor unfamiliarity with nitrite it may be safer to use nitrate.

The Panel next addressed question 2--possible changes in initial nitrite levels. Dr. Greenberg outlined the currently allowed levels of nitrite: 156 ppm for chopped product, 200-211 ppm for pickle-cured product, and 624 ppm for dry-cured product. Citing Dr. Jonathan White's comments before the Panel regarding source impact of human nitrite consumption, he emphasized that, while nitrite could be reduced somewhat, he questioned if the possible loss in botulinal safety would offset any benefit in the resultant small reduction in nitrite consumption. Dr. Weisburger pointed out that the data show that 100 ppm of nitrite was sufficient for botulinal protection in cooked sausage. Dr. Greenberg emphasized that the botulinal data could not be interpreted on a strictly quantitative basis and demonstrated simply that the higher the nitrite level at time of formulation, the greater the botulinal safety. He emphasized the particular need for maintaining the current industry formulation

levels for nitrite in canned perishable or shelf-stable product. Turning to pickle-cured product, the Panel was asked by Dr. Seideman, Wilson and Company, to target for 156 ppm rather than set that level as a maximum. Dr. Draudt, Peter Eckrich and Sons, reminded the Panel that levels of nitrite in corned beef may drop quite low before the product is cooked in the home. Jack Hohhof, John Morrell and Company, related the difficulty processors have in stabilizing the color and flavor in corned beef hash.

Other categories of product were discussed as the Panel formulated its second recommendation. All product categories, except dry cure and bacon, were to be limited to 156 ppm of nitrite introduced into product; the product categories involved were: cooked sausage, canned cured perishable of shelf-stable product, fermented sausage, pickle-cured products except bacon, cured sterile canned product. The Panel deferred action on dry cure and bacon because data is currently being developed in cooperative industry-government studies.

The Panel next considered question 3--to reduce permitted residual nitrite levels. Dr. Foster, University of Wisconsin, pointed out that there is not a practical advantage in reducing the residual nitrite because we may increase the risk of botulism. After some discussion, Dr. Weisburger proposed that, except for dry cure and fermented sausage which may still contain nitrate, the residual nitrite of all products be reduced to 100 ppm. Mr. Hohhof expressed concern that the packer faced with a limit of 100 ppm residual would introduce less than 156 ppm of nitrite initially. The Panel discussed the residual nitrite levels by product category and recommended: cooked sausage--100 ppm; bacon--no action pending current study; canned cured perishable or shelf-stable product--125 ppm; pickle-cured products except bacon--125 ppm; fermented sausage--no action, pending nitrate-need study; canned cured sterile product--50 ppm; dry-cured products--no action, pending nitrate-need study.

Dr. Keating voiced strong opposition to the lowering of nitrite and the removal of nitrate because safety has been demonstrated at the current levels of use. He said:

> I'm concerned about spoilage, about poisoning kids with food that has had a worthwhile preservative taken out of it on the basis that it might cause cancer. I think some recognition might be given that safety is right where we are--present data does not make it possible to know where safety lies. I get concerned because botulism is a startling thing--people die. If you make wieners with less nitrites or nitrates and Mrs. Brown takes them home, and her refrigerator is not the best and her kids come in with diarrhea, that's not botulism but it's bad for the kids. We don't have any data on spoilage and how important our traditional methods of preserving are in relation to food poisoning--staphylococcal and

salmonella food poisoning. Instead, we have a total focus on the possibility that there might be danger to someone, sometime from cancer. The general consensus of this group is that down is good, but it's not a universal feeling. I still say we've got to have considerable reservation about the reduction of traditional preservative methods in meat on the basis of the information provided to the Panel.

Dr. Mussman responded to these remarks by saying that the preliminary recommendations formulated during the day's discussions, although recommending reductions in both nitrate and nitrite usage, were not such that they would compromise safety. In each instance, they were representative of what is achievable today and, in fact, are a reflection of what a great number of processors are doing now. Implementation of the recommendations would simply bring uniformity to processing and recognize that earlier permitted nitrate and nitrite levels were no longer applicable.

No action was taken on questions 4 and 5, but Dr. Weisburger asked if there was any product(s) in which nitrite is currently used that should be disallowed? No one was able to respond to the question at that time. Dr. Mussman concluded the meeting with remarks about the status of these recommendations by the Panel. They are recommendations to the Secretary of Agriculture. If the recommendations are accepted, proposals to amend the regulations will be published in the Federal Register and comments will be invited during a comment period.

The next Panel meeting will be held on September 9, 1974. The meeting was adjourned at about 3:30 p.m.

The Fifth Meeting - September 1974

The fifth meeting of the Secretary's Expert Panel on Nitrite and Nitrosamines was convened at 9:39 a.m., September 9, 1974, in Room 2096 of the South Agriculture Building, 14th Street and Independence Avenue, SW., Washington, DC 20250. There were 52 persons and 5 panel members in attendance.

Dr. Harry C. Mussman, Executive Secretary, opened the meeting and summarized the three recommendations of the previous meeting. Briefly, the recommendations were:

1. Nitrate use be discontinued in all products except dry-cured products and fermented sausage--these exceptions were made because of the lack of information on the role of nitrate in these products,

2. Nitrite be reduced to 156 ppm ingoing except for dry-cured products and bacon--it is possible that, pending new information, some other level of nitrite usage will be recommended by the Panel for the excepted products,

3. Residual level of nitrite be limited to: 125 ppm for pickle-cured and canned perishable or shelf-stable cured products, 100 ppm for cooked sausages, and 50 ppm for canned cured sterile product--no change was recommended for bacon, fermented sausage and dry-cured products at this time. Dr. Mussman asked if there were changes or amendments to the minutes of the July 15 meeting. Dr. Greenberg had previously offered several changes that are to be incorporated.

The matter of nitrate was discussed by Dr. Weisburger, who concluded by relating his experiences with high levels of nitrite/nitrate in a stew held at room temperature for several days.

Mr. Ron Fouche', representing the Lebanon Bologna Institute, described the procedure for making lebanon bologna--a fermented beef sausage, which normally has a finished product pH of 4.5 to 4.7. Fouche' stated that nitrate is the only curing agent besides salt that is used by many processors in making this product. The finished product residual nitrite is usually less than 10 ppm. In response to questioning, Fouche' noted that: (1) residual nitrate varies from 600 to 800 ppm; 2) product does not need refrigeration and; 3) during storage the nitrite level remains constant and the nitrate level decreases slowly. Fouche' demonstrated the results of preparing product with nitrite only by showing product in a pliofilm bag that demonstrated excessive moisture loss and gas production. Unfortunately, the microorganism(s) causing the fermentation failure were not identified. Mussman directed the Panel's attention to an intra-departmental memorandum dated September 6, 1974, that showed wide variability in the levels of nitrite

and/or nitrate used by lebanon bologna producers. The Panel indicated that during the next 2 years, scientific data should be carefully gathered to justify further the use of nitrate in fermented sausage.

Dr. Steven Tannenbaum, Massachusetts Institute of Technology (MIT) researcher, discussed his studies on saliva that indicated wide variability in salivary nitrite content. He stated that Dr. White's estimate of salivary nitrite at 7½ mg/day should be raised to 9 to 12 mg/day based on his studies. Tannenbaum noted that high levels of nitrate in drinking water did not affect his personal salivary nitrite level. Also, he stated that nitrosamines will form at neutral pH as well as at low pH--their formation is dependent upon temperature, concentration, pH, and presence of nitrite and certain amines.

After lunch, Dr. T. N. Blumer, North Carolina State University professor, presented data from studies on dry-cured hams and loins in which various organoleptic properties were evaluated. Use of salt and sugar alone produced a surprisingly good product as measured by appearance, color and aged flavor, but at 90 and 100 days the nitrite or nitrate and nitrite cured hams had better color and slightly better aged flavor than products cured with only salt and sugar. In a model meat system, there was very little loss of nitrite at 4° C., but at 29° C. (84° F.) nitrite disappeared rapidly. The North Carolina study also involved dry-cured pork that received 10, 40, 70, 100 or 130 ppm nitrite. At less than 70 ppm nitrate, loins had poorer cured color at 16 days than loins with 70, 100 or 130 ppm nitrite. No significant difference in flavor was detected by a taste panel when loins were cured with 70 to 130 ppm nitrite. In response to questions, Blumer affirmed that: (1) no nitrate was needed if 70 ppm or more nitrite is used; 2) 70 ppm nitrite gives adequate color and flavor to ham and cured loins.

Ms. Marian Burros, Washington Post reporter, expressed interest in cured products prepared without nitrite or nitrate and asked if the Panel was going to study these? Dr. Mussman replied that the production of salt-cured products is extremely small in volume and that clearly the large volume products are nitrite and nitrate cured; thus the panel should direct its attention to these products, and develop recommendations on nitrite and nitrate use which will reduce any potential hazard to a minimum.

Dr. Edwards asked her fellow Panel members to recommend that curing agents and cured meats not be permitted in infant and toddler foods. It was explained that no nitrite or nitrate is used in infant foods and that cured products had only limited use in toddler foods. Mussman pointed out that toddlers often eat from the table and could easily be offered frankfurters, ham or other cured products, thus any nitrite/nitrate in toddlers' foods would seem to be of little significance to the toddler diet. Dr. Keating confirmed that above 6 months age, the infant has no problem with methemoglobinemia from cured meats and that nitrates

associated with this problem come primarily from vegetables. The Panel was asked to supply the Executive Secretary with comments on Dr. Edward's proposed recommendation.

Dr. Mussman, turning the discussion to ascorbate, outlined the effects of ascorbate as follows: 1) blocks the formation of nitrosamine from nitrite, 2) reduces residual nitrite, and 3) at high levels reduces botulinal protection. A study at Wisconsin showed that at levels greater than 1,000 ppm, the protection against Clostridium botulinum growth afforded by nitrite is markedly reduced by ascorbate. The Panel believed that there was insufficient information on the effect of ascorbate to justify a recommendation at this time. Perhaps the current bacon study will provide additional information.

Next the discussion centered on fermented sausage and the difference between lebanon bologna and fermented sausage (thuringer) recently studied by the American Meat Institute, FDA and USDA. It was estimated that lebanon bologna represents about 20 million of the 500 million pounds of fermented sausage produced annually in the United States. Pork roll produced exclusively by two firms is actually a fermented sausage made from pork, salt, sugar and nitrate, and has a nitrite residual much like lebanon bologna. Greenberg emphasized the Panel's concern that nitrite could come from nitrate. The Panel indicated it will assume that nitrate is needed pending results of new studies. Panel members will supply to the Executive Secretary their thoughts regarding questions which need answers in the nitrate area. This information will be passed on to the fermented sausage and dry-cured product industries for development of the required data.

Dr. Mussman summarized the meeting by indicating that the previous recommendations of the Panel will stand and that a new recommendation would be considered--that recommendation was to discontinue use of nitrite, nitrate, or cured meat in infant and toddler foods. The three tentative recommendations which were finalized by the Panel will be circulated to the Panel members for concurrence before being forwarded to the Secretary of Agriculture for his consideration.

The next panel meeting will be held in February or March 1975. The meeting was adjourned at about 3:20 p.m.

The Sixth Meeting - March 1975

The sixth meeting of the Secretary's Expert Panel on Nitrites and Nitrosamines was held on March 28, 1975, in Room 218A of the Agricultural Administration Building on Independence Avenue at 12th Street, SW., Washington, D.C. The meeting was convened at 9:45 a.m. by the Executive Secretary, Dr. Harry C. Mussman, Acting Associate Administrator of the Animal and Plant Health Inspection Service. Panel members present included Drs. Wasserman, Keating, Schaffner and Greenberg. There were 26 persons in attendance in addition to the Panel and the executive and recording secretaries.

Dr. Mussman opened the meeting by highlighting the five previous meetings. He introduced Dr. Robert M. Schaffner, Associate Director for Technology, Bureau of Foods, U.S. Food and Drug Administration, who was appointed to fill the position held by the late Dr. Leo Friedman. Mussman invited comments from the Panel and the floor concerning the minutes of the previous meeting. There being no comments, the minutes were accepted as written.

Dr. Mussman discussed the status of proposed rulemaking that will propose changes in the regulations on nitrate and nitrite in response to the three recommendations of the Panel. He clarified the Panel's intent not to set a minimum ingoing level of nitrite, but rather to set a maximum level of 156 ppm nitrite and allow lower levels of nitrite for products that research and/or experience has shown can be made safely with less nitrite. Dr. Wasserman pointed out that the Panel did not discuss cures in poultry products. It was explained that there was only a small number of cured poultry products and it seemed logical to set similar requirements for poultry products. Dr. Schaffner commented that FDA published its proposal on nitrates and nitrites in November 1972 and has been waiting for USDA's proposal before publishing their final regulation.

Dr. James Keating, Panelist, spoke on nitrite toxicity and methemoglobinemia studies with infants. He indicated that nitrate ingested by the infant under 3 months of age may be converted to nitrite by stomach bacteria and could cause methemoglobinemia. This was particularly true in infants suffering from severe diarrhea. He said that half the reported cases were traced to nitrate in well water and half to nitrate in vegetables. Keating related the case history of a methemoglobinemia illness caused by consumption of home-prepared carrot juice from carrots with a high nitrate content. According to Keating, Gerber Foods has not found nitrosamines in infant foods. He concluded by saying that there is not significant danger from methemoglobinemia among infants greater than 1 year of age and that 90 percent of the cases occur among infants less than 3 months of age.

Dr. John Birdsall, Scientific Director for the American Meat Institute, reported results of the joint Industry-FDA-USDA studies on bacon and country ham. He said that three of the 20 country hams purchased at retail had detectable nitrosamine, containing 16, 20, and 50 ppb nitrosopyrrolidine when a ¼ inch slice was fried at 340° F. for 6 minutes on each side. There was no relation between residual nitrate or nitrite levels and the presence or level of nitrosamine. Later, when slices of the positive nitrosamine hams were either fried for 3 minutes on each side, boiled or tested raw, they had no detectable nitrosamines. It appears that the longer period of frying induced nitrosamine formation.

Dr. Birdsall summarized the bacon study by saying that test samples (made with 120 ppm nitrite and 1,000 ppm erythorbate) had detectable nitrosamines even though the low nitrite and high erythorbate treatment had a beneficial effect in reducing the level of nitrosopyrrolidine. Levels of this nitrosamine ranged from 14 to 19 ppb for control bacon and from less than 10 ppb to 14 ppb for the test bacon. He emphasized that to reduce the chance for nitrosamine formation, most larger packers are using the maximum level of erythorbate or ascorbate allowed by regulation and urged that all processors of bacon be encouraged to use the maximum allowed cure accelerator to reduce this potential hazard. Mussman pointed out that no nitrosamines have been found in raw bacon or country ham.

One of the Panel's recommendations of July 15, 1974, had been to defer action on nitrate in fermented sausage. Mussman read a letter addressed to the Lebanon Bologna Institute that asked six questions the Panel would like answered to help in its deliberation over the continued use of nitrate in fermented sausage. Mr. Ron Fouche', the Institute's spokesman, replied by saying that the Eastern Regional Research Center, ARS, USDA, had not found any of six volatile nitrosamines in lebanon bologna and that this answered one of the questions. Wasserman commented that just because nitrosamines were not found is not sufficient justification for the high nitrate level--the intent is to reduce the environmental incidence of nitrate. The Institute members, according to Fouche', believed that studying their products and processes to seek answers to the other five questions was too expensive. Again, the services of the ARS laboratory at Philadelphia were offered.

Lebanon bologna is usually formulated with 1,500 to 1,700 ppm of nitrate and with 0 to 156 ppm of nitrite. Fouche' reported that finished lebanon bologna ready for shipment and held at 35° C. (95° F.) for up to 3 days, averaged less than 1,000 ppm residual nitrate and less that 10 ppm residual nitrite. He said that no processor is using only nitrite to cure this sausage and that when only half the normal 1,700 ppm was used, the product was "grey" or "rawish." It was pointed out by the Panel that other processors of fermented sausage (e.g., summer sausage) have performed needed studies, and that such studies should be done on lebanon bologna and data accumulated for review by the Panel.

Mussman asked Mr. Fouche' to respond to the letter containing the Panel's questions, indicating those he felt need not be answered along with appropriate reasons. With this response the Panel could determine further actions needed.

Dr. Mussman directed the Panel's attention to the letter from Dr. Norton Nelson, New York University Medical Center, about a preservative added to Japanese fish sausage. The preservative known as "AF2" (believed to be furylframide) has been determined to be mutagenic and carcinogenic. Dr. Nelson said the Japanese felt that AF2 should be removed, but he questioned whether their consideration of nitrite as a substitute is appropriate. The USDA will discuss the matter with Dr. Nelson.

Dr. Mussman read excerpts from an ARS, USDA, memorandum about nitrosamines recently found in souse, head cheese, and blood and tongue sausage. Dimethylnitrosamine was detected at levels from 3 to 63 ppb in retail samples of souse or headcheese. One souse sample also contained 19 ppb of nitrosopyrrolidine. The ARS study was conducted because these meat products contain nitrite along with meat ingredients; e.g., skin, snouts and tongues that are high in connective tissue. Connective tissue is an excellent source of the amino acid, proline, which could be a precursor of nitrosopyrrolidine. USDA has requested industry's help in research on this new nitrosamine finding.

Monsanto Chemical Company, in a letter to the Panel, asked that they consider replacing part of the nitrite in cured meats with sorbic acid or its salt. The Meat and Poultry Inspection Program has considered sorbic acid primarily as a mold and yeast inhibitor and permits its use on casings to decrease mold growth on dry sausage. When used as a preservative in product, it may mask spoilage or prevent normal spoilage characteristics. Nitrite is unique in that it not only imparts color, flavor and texture, but also protects product against the hazard of C. botulinum. Monsanto's data showed some delay of can swelling when 1,000 ppm of sorbic acid was added to ground ham inoculated with C. botulinum spores at 1,000/gm. Monsanto indicates that preliminary incubation studies on canned product comparing the inhibitory qualities of nitrite alone compared with those of reduced levels of nitrite plus sorbic acid are promising enough to warrant further study. A Swift and Company study in 1974 showed a growth-retardant effect on other pathogens when sorbic acid was used. Monsanto plans to continue its studies and will keep the Panel informed.

Dr. Greenberg highlighted the recent FDA-USDA Task Force Meeting on Nitrates and Nitrites held February 10 citing Tannebaum's work on salivary nitrite, the finding of dimethylnitrosamine in unfiltered cigarette smoke, and the finding of type B botulinum spores in 8 of 180 bacon samples in Great Britain.

Questions from a Georgetown University law student centered on what has happened in Norway with its "ban" on nitrite and why not produce meat products that do not contain cures? It was disclosed that the Norwegian government has granted numerous exceptions, due to the need for botulinum protection, for most cured products except for their frankfurter-like product. They determined that its method of merchandising and handling is such that nitrite is not needed for botulinal protection. The Panel noted that in France the major cause of botulinal cases today is from home-cured hams. Dr. Schaffner clarified the prior sanction exemption for nitrite: its use predates the 1958 amendment to the Food, Drug and Cosmetic Act. Here, considering the benefit/risk ratio, we are more concerned with the hazard of botulinum than with the risk of nitrosamine formation according to Schaffner.

The Panel answered several other questions from the floor by stating that: (1) refrigeration and freezing of product was inefficient, impractical and inadequate; (2) there is no known substitute for nitrite at present; (3) product completely sterilized in the can is almost unsalable because of loss of palatability; (4) other countries follow the lead of the U.S.; thus the Panel has the responsibility to study all aspects of the question and; (5) to ban nitrite before the research answers are clear could be disastrous.

The meeting was concluded at approximately 3:10 p.m. No date was set for the next Panel meeting.

The Seventh Meeting - December 1975

The seventh meeting of the Secretary's Expert Panel on Nitrites and Nitrosamines convened at 9:45 a.m., December 10, 1975, in Room 218A, Agriculture Administration Building, Washington, D.C. The Executive Secretary, Dr. Harry C. Mussman, opened the session by re-introducing the Panel members. Present were Drs. Cecile H. Edwards, Richard Greenberg, Robet Schaffner, A. E. Wasserman, and John H. Weisburger. The sixth panel member, Dr. James P. Keating, was unable to attend. Fifty-six people were in the audience. Mr. Irwin Fried transcribed the minutes of the meeting.

In his opening remarks, Dr. Mussman restated the purpose of the Panel. It was a forum for the experts to share new ideas and exchange views and to call upon individuals with known expertise. Initially the Panel meetings used prepared talks to set the stage for future meetings. At this point, however, only occasional prepared presentations are contemplated.

He also stated the general philosophy of the Panel which was to present and discuss, insofar as possible, a balanced view of all information; a full airing, both pro and con, that would get the complete story to the public so that they could better understand the situation, participate where desirable, and accept decisions as they were made.

First on the agenda was a Panel discussion of the manner in which their three recommendations were addressed in the nitrite proposal published in the Federal Register on November 11, 1975. In addition, Dr. Mussman asked the Panel to give its views on the special proposal added expressly for bacon.

Dr. Greenberg suggested that the proposal should have included the fact that dry-cured products and fermented sausages would be dealt with within a 2-year limit.

The Executive Secretary stated that since the Panel, researchers, and others were aware both of the problem and the time limit, there was no need to make reference to these products in the proposal. He remarked that the time limit referred to would be measured from the first time reference was made to the subject in the minutes of the previous meetings.

A member of the audience questioned the need for nitrite in cooked meat products. The answer by Dr. Greenberg was that many meat products were not cooked to sterility, and in the home, moderate cooking would not necessarily inactivate preformed toxin. He cited an as yet unpublished work under the direction of Dr. E. M. Fester of the Food Research Institute that will add to the store of knowledge on that particular problem.

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MINUTES OF THE SEVENTH MEETING OF THE EXPERT PANEL ON NITRITES AND NITROSAMINES

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Dr. Edwards added that bacon has various uses in America and is frequently used as seasoning, getting only a brief boil. The inference, again, was that preformed toxin, if present, might not be inactivated.

The use of salt as a preservative was then discussed. An error in the proposal was pointed out in that it defined brine concentration as salt divided by moisture; whereas in reality it was salt divided by salt plus moisture. An audience question concerned the effectiveness of salt alone as a preservative.

In answer to the question, Dr. Greenberg cited a study which showed that a brine concentration of 6.5 to 8 percent in combination with a low nitrite input was sufficient to stop putrefaction, but not botulism. The danger of this situation is that no evidence of spoilage is present to warn a consumer against eating the potentially contaminated food. A brine concentration of 8.5 percent or higher with no nitrites offered

protection against all types of spoilage, but presents problems insofar as palatability is concerned. Additional treatment of the product, such as long soaking in the home, is necessary prior to preparation.

Another problem associated with the use of salt alone is the difficulty of achieving uniform penetration of salt in solid pieces of meat. The danger here is the presence of "pockets" in the meat which would support bacterial growth.

Dr. Edwards also suggested that the role of excess salt is a health consideration, especially in respect to hypertension. Dr. Weisburger stated that he not only shared Dr. Edwards' concern, but in his view, high salt intake presents a more important health risk than the low levels of nitrosamines found in bacon.

Dr. Mussman points out the impossibility of finding any one easy solution to the problem at hand, each proposed solution seemingly leading to more problems.

Dr. Mussman then asked for opinions on the proposed ban on the use of cover pickle, noting that it was difficult to control the input of nitrite that way, but a problem existed in that some products did not lend themselves to other methods of curing.

Dr. Wasserman said he was cooperating with a group studying the possibility of controlling nitrite input while using cover pickle. No data is available as yet. Several industry representatives stated their concern that cover pickle would be banned. They were told to be sure to get their comments on the record. Dr. Mussman added that the final rulemaking could conceivably exempt certain products, and comments concerning cover pickle use would be given careful consideration.

Dr. Mussman then directed the Panel's attention to the question of the banning of nitrite in infant and junior foods, but not in toddler foods.

Dr. Edwards stated she favored the complete ban of nitrite in children's foods. Although it was true that toddlers were of an age where they ate from the table, people who avoided nitrites still found many uses for commercially prepared toddler foods.

At this point, Dr. Michael Jacobson of the Center for Science in the Public Interest asked for and received permission to enter a prepared statement into the record. Some of the items he covered included the slow pace at which the Panel was operating, his belief that the Panel was illegal in that it had no consumer member; the thrust of the deliberation which seemed to be to leave nitrites in food rather than eliminate nitrosamines; his concern over the use of nitrite strictly as a cosmetic; the ban in baby foods, whereas in fact they had voluntarily been eliminated; and why other preservatives such as salt, sorbitol, high heat, etc., were not being considered.

Dr. Mussman stated that in light of the agenda, and the limited time available, it was impossible to answer each of the charges made by Dr. Jacobson, and in addition many had been discussed at previous Panel meetings.

Some rather heated exchanges followed with the Panel referring to specific data and asking Dr. Jacobson to produce data to which he alluded. He agreed to supply Dr. Weisburger with data at a later date.

Another question from the audience asked why the necessity for nitrite in canned ham. Dr. Greenberg pointed out that canned ham did not receive a sterile cook, and if it did it would be inedible because of color, texture, and other organoleptic changes.

In answer to another question, Dr. Weisburger pointed out that there were hundreds of known nitrosamines. The one prevalent in bacon,

nitrosopyrrolidine, caused liver tumors in animals. Projecting this to humans, he made the point that liver cancer is not prevalent in America, nor has the incidence changed appreciably since records were first maintained. He felt that this type of evidence was more important to him than the fact the nitrosopyrrolidine was a carcinogen in laboratory animals.

After noting that the types of speculative arguments taking place were not productive and the Panel's purpose was to share and elicit information, Dr. Mussman suggested a discussion of the bacon section of the proposal.

Dr. Schaffner expressed approval of the move to a 125 ppm nitrite limitation for bacon, but pointed out the possible danger of lesser levels unless combined with another preservative. He gave an outline of the latest FDA survey of bacon in Washington, D.C., stores which found a range of 5 to 47.5 ppb of nitrosopyrrolidine, with most samples in the teens. Twenty-one samples were in the survey and none were negative. Only in experimental bacon packs were negatives found.

A discussion followed on how closely the use of nitrite was controlled in actual practice. The present regulation only places a limit on the maximum amount and the feeling was that industry at this time was using close to the maximum.

Dr. Mussman expressed the opinion that not only was it important to reduce the ingoing nitrite to 125 ppm but also to combine it with the maximum amount of 550 ppm ascorbate or erythorbate, and that it was of utmost importance to exert close control over the entire pumping process. Data indicate that when closely controlled, the 125 ppm of nitrite and 550 ppm of ascorbate or erythorbate were reducing or eliminating the formation of nitrosamines. Another important consideration is that as we reduce the maximum permissible nitrite, we may have to set minimums as well. With regard to questions concerning alternate procedures to nitrite curing, Mussman noted that freezing or sterilizing by heat

required large energy inputs and processing facilities that were unavailable at this time.

Dr. Birdsall of the AMI presented the latest data on the joint FDA-USDA, industry study on bacon and country hams. He also corrected some data on average daily human nitrite intake from all sources and presented the protocol for the latest cooperative study in bacon.

Dr. Richard Lechowich, Head of the Food Science Department of Virginia Polytech Institute (VIP) presented a protocol for a study of the role of varying amounts of nitrite, nitrate and salt in the production of country hams. This is a study which will impact on the actions which may take place on dry-cured products in the future.

Dr. Tannenbaum of Massachusetts Institute of Technology (MIT) presented the results of studies of nitrite and nitrate in saliva and the effect of various foods and amounts of food on its content.

Dr. Mussman then referred to a study received from the Lebanon Bologna Association, but which arrived too late to analyze for the meeting. He asked the Panel to study it and proposed it as a subject of the next Panel meeting.

Dr. Wierbicki from Natick Laboratory referred to their radiation studies and the seeming necessity for the presence of nitrate. He asked that he be given an opportunity to address the next meeting of the Panel.

Another question from the audience referred to the question of types of cancer prevalent in certain countries, and whether work had been done to determine if eating patterns, environment and other factors had been analyzed to determine their effect in certain sections of any one country, the USA in particular.

Dr. Wasserman answered by saying that this was what research was all about, but the time interval involved in such research is so long that conclusions are necessarily slow, and difficult to define in absolute terms.

Dr. Mussman then concluded the session by thanking the Panel and audience. He believed that the exchange of information was useful and would help in a fuller understanding to the problems involved. He emphasized the urgency of the new bacon study and reiterated the necessity of addressing the fermented sausage and dry-cured products questions. He again stated that the minutes of the meeting and the formal presentations would be made available to all and in addition would be made part of the official comments on the nitrite proposal. The texts of the formal presentations would also be included in the copy of the minutes filed with the Hearing Clerk. While no time was set for the next meeting of the Panel, he suggested that another would be held in 3 or 4 months.

The Eighth Meeting - April 1976

The eighth meeting of the Secretary's Expert Panel on Nitrites, Nitrates, and Nitrosamines was convened at 9:30 a.m., April 28, 1976, by Dr. Harry C. Mussman, the Executive Secretary. He introduced the Panel members to the audience. In bidding the audience welcome, he expressed pleasure at the number of people in attendance and set ground rules for their participation. He stated that the purpose of the meetings were to provide for an exchange of new information, the presentation of latest research, and updates of matters held over from previous meetings. The format of the meetings was essentially that of a forum for discussion and evaluation by the Expert Panel of information and new research data presented to it. Time would be available for questions and comment from the floor.

Dr. Mussman asked the Panel for approval of the minutes of the previous meeting. They were accepted as submitted. After reviewing the day's agenda, he briefly summarized for the Panel the history of the USDA-FDA interagency nitrosamine work group.

He mentioned that he co-chaired the USDA-FDA joint work group which last met in March. It had started as a small group holding relatively closed meetings to discuss nitrites, nitrates, and nitrosamines and share hypotheses. The meetings have gradually increased in size and have become a clearing house for evaluating preliminary research results. Dr. Blumenthal, who replaced Dr. Friedman on the work group has expressed the feeling that the meetings have now outlived their usefulness, in that several international symposia are being held. Dr. Mussman, however, expressed concern at the idea of disbanding. At the last meeting, sixty people and representatives from five countries were present. He asked the Panel to make its feelings known regarding the future of this work group.

Mr. Irwin Fried, the Recording Secretary, presented a review of the comments received on the nitrite-nitrate proposal. He reported that the 338 comments had been divided into various categories for ease of handling.

Category 1 - Forty-three (43) comments offered unqualified support of the proposal. Some explained their reasons on the basis that such regulations were needed because of public health concerns.

Category 2 - Another 29 comments also approved of the proposed action with explanations offered such as considerable research and study has been conducted, and that a carefully planned approach was preferred over an arbitrary and poorly founded one.

One typical example observed that the proposed ban on nitrate was good, but that further study was needed concerning its use in fermented and dry cured products; that the proposed ban of nitrite in infant and junior food was good; that the same proposed rules should be applied to poultry products; that the use of nitrites in such items as frankfurters could be omitted provided the product was carefully handled to prevent the growth of Clostridium botulinum. The respondents recommended that the final regulation be written so that future changes could be made as research confirmed the safety of such proposed changes.

Category 3 - Another group of 38 comments generally supported the proposal but expressed various reservations. They were made by the industry and dealt with technical problems in controlling the amounts of nitrites.

Category 4 - There was another group of comments (63) which contained statements that neither supported nor opposed the proposal, but which made observations or suggestions.

1. Some of the observations questioned the Department's sincerity in its approach to dealing with the nitrite question; some alluded to personal fears related to their health and that of their children; a few expressed wonder as to why all "chemicals" weren't totally banned; a few recommended that all "chemicals" should be banned; and some simply state that in purchasing meats they avoided cured meat products.

2. There were several comments suggesting that lowering the levels of nitrite usage was desirable and that the levels should be further reduced. Some indicated that reduction should occur only if scientific evidence supported it, and they expressed hope that appropriate studies would continue.

3. A few comments questioned the need for nitrite in some canned products indicating that it was used as a substitute for good hygenic practices. The Expert Panel considered the question of need, and the proposal reflects their considerations and recommendations.

4. A few of these 63 comments expressed some degree of reservation about reducing the levels of nitrite and increasing any risk of botulism. A few others appeared to express stronger feelings by suggesting that no reductions in usage levels should be effected unless a substitute for nitrite is found that provides the needed antibotulinal properties. A few suggested that since there is no evidence to prove that curing agents present a problem relating to humans, that no action is warranted.

5. At least one comment in this category directly addressed the relationship of the Delaney Act to this rulemaking.

6. Three of these 63 comments suggested that some kind of labeling be placed on certain products to indicate that a risk of danger to one's health might exist from eating such products.

Category 5 - There were 47 comments addressing the proposed ban on immersion curing, and 2 concerning the provision to recognize salt as a curing agent, with preservative properties.

With respect to the proposed provision for salt, there was apparently some miscommunication and misunderstanding. The intent was to officially list salt as a curing agent, and to establish appropriate levels of salt when it is used as a preservative.

Category 6 - There were 101 comments which in general recommended that the use of nitrates and nitrites be banned.

1. Several comments in this category advocated a complete ban on the use of nitrate and nitrite in meat and poultry products. None offered any new scientific evidence in support of the comments.

2. There were a few of these 101 comments which, beyond their comment to ban the use of nitrite in meat and poultry products, suggested that other additives, such as ascorbic acid, could be used to accomplish the same result as nitrite.

3. In many comments, not only in this category, but in others, suggestions were made that salt, smoking, heat processing and a greater reliance on refrigeration could serve the same purpose as nitrite.

4. Some of the comments in this group suggested that the use of nitrite should be discontinued because it causes cancer and is therefore illegal under the Delaney Act.

5. One comment presented, at least in part, the views of five organizations. They requested, among other things, that the Department ban the use of nitrate and nitrite in all cured meat products and toddler food; that one year exemptions be given to processors during which time they would be required to develop the technology to prepare product with little or no risk from Clostridium botulinum; and that during the one year period, labeling be affixed to products containing nitrite to inform the consumer that a health hazard is involved.

Category 7 - The last category of 11 comments opposed the proposal for two general reasons. First, it was stated that there was not sufficient information to assure a finished product safe from botulism, and that no evidence exists to indicate any imminent public health hazard because of nitrite. Second, they felt the proposal was too complicated and small operators would be forced out of business because they couldn't understand it.

One comment of special interest came from the Director, Office of Consumer Affairs, Department of Health, Education and Welfare. Several points were identified as weaknesses in the proposal's statement of considerations. These included: (a) insufficient discussion of the public health significance of nitrosamines; (b) whether nitrosamines formation in bacon could be obviated by methods of cooking other meat products besides bacon; (e) the relationship of the rulemaking as it relates to nitrosamine formation and the Acts administered by USDA and FDA; (f) whether other additives could be used in lieu of nitrite; and (g) discussion of the functionality versus safety of nitrite.

Because of insufficient discussion of at least these items, the comment suggested that the consumer did not have all the needed information upon which a responsible comment could be prepared and submitted.

Dr. Mussman then asked the Panel to review the final rulemaking when ready, and to make any comments which they felt to be appropriate. Meanwhile, a discussion was held by Panel members on some of the provisions of the proposal itself.

The question of salt in particular, was one which disturbed Dr. Weisburger. The 10 percent brine concentration recommendation in lieu of the use of nitrite was hazardous in his opinion. The risk of hypertension and its proven correlation with high sodium intake was of more significance to him than the potential danger from the use of nitrites.

Dr. Wasserman pointed out that the 10 percent was not a requirement but rather a recognized preservative level. Salt could continue to be used in cured products at condimental levels. Dr. Weisburger said that a study would be appropriate to determine the eventual problem. Studies in Japan have shown significant correlation between high salt intake and hypertension.

The question of the preservative value of smoke was raised. The Panel agreed that both the color produced and the preserving qualities were derived from the oxides of nitrogen present.

On the question of nitrites in baby foods, Dr. Keating pointed out the Panel was discussing banning nitrites in the meat ingredient, not in the total food. Nitrite were present in many of the vegetable ingredients.

Dr. Edwards, Head of the School of Human Ecology, Howard University mentioned that a question had been asked at the last meeting concerning differentiation of the various classes of baby foods. She had gathered some information which she presented to the Panel and audience. In 1935, the normal age for babies to start solid foods was considered to be six months, and consisted of cereals, meat etc. By 1954, 80 percent of all pediatricians favored starting solids prior to 3 months, and

66 percent, prior to two months. More recently, the age has shifted to 1-2 months and even lower. In an overall evaluation, Edwards felt that strained infant foods were for use as soon as needed, with a switch to junior foods (larger particle size) at 7 to 9 months; and then toddler foods when the child was old enough to eat from the table, or at start of walking. Dr. Keating added that individual mothers' actions, dependent on instinct and traditions, had proven to be quite a successful system.

Dr. Keating pointed out the necessity for accurate reporting on the part of the news media. He observed that the vast majority of people receive their information on vital issues from the press, and unless reporting was completely accurate and unbiased, there was great potential for increasing anxiety on the part of conusmers, where no valid reason for such anxiety existed.

Dr. Mussman concluded the discussion by saying that the use of nitrites in the meat portion of toddler foods would be given careful consideration, but asked the audience to keep in mind that the ingestion of nitrates from water, fruits, and vegetables would still provide a source of nitrite in the diet. He then introduced Dr. Ronald C. Shank, University of California who presented a paper titled "Dose-Response Study of the Carcinogenicity of Dietary Sodium Nitrite and Morpholine in Rats and Hamsters." The work was done in conjunction with Dr. P. M. Newberne at the Massachusetts Institute of Technology. It was published in "Food and Cosmetics Toxicology," Vol. 14, pp. 1-8, Pergamon Press 1976.

In summing up the paper, Dr. Shank stated:

A dose-response study of the carcinogenicity of dietary sodium nitrite and morpholine in rats demonstrated production of hepatocellular carcinomas and liver and lung angiosarcomas at concentrations as low as 50 ppm each of sodium nitrite and morpholine. In addition, rats given a diet to which was added 1000 ppm sodium nitrite alone, developed an elevated incidence of lymphoreticular tumors over the no-additive control value. Hamsters were less sensitive to the carcinogenicity of dietary N-nitrosomorpholine and sodium nitrite and morpholine.

The paper presented by Dr. Shank was highly technical in nature and aroused many questions and comments by the Panel. Some of the more pertinent questions were:

1. Was any N-nitrosomorpholine found in the diets, other than in those to which it was added directly? Dr. Shank's answer was that it was found only in those diets containing the 1000 ppm of both nitrite and morpholine, and then only at the 1-2 ppm level. An interesting fact was that this diet produced more tumors in the test animals than the diet containing 50 ppm of N-nitrosomorpholine. The conclusion was that the 1000/1000 diet produced more than 50 ppm of N-nitrosopropholine and

since it was not found in the diet except at very low levels, the nitrosation was in all probability taking place in the stomach.

2. What implication is present for humans? Dr. Shank gave a detailed explanation of the time period involved in production of nitrosamines under proper conditions of acidity, and presence of available nitrite and suitable amines. He said that present indications were that the reaction must be metabolically activated if it is to take place in the stomach and that evidence suggests that man has the mechanism to do it.

3. Has there been any epidemiological evidence of cancer in man caused by high nitrite and amine exposure? Dr. Shank answered that there is an extremely high death rate from esophygeal cancer reported from the North of China. The environment is reported to be high in nitrites and nitrates. In the study, examination of food and stomach contents showed a significant relationship between the presence of three fidderent nitrosamines in areas of high cancer incidence, and practically no nitrosamines found in the food or stomach contents in areas of low cancer incidence. The unfortunate part of the study is that the analytical work is questionable and there is very little chance of outside investigators being able to repeat the study to confirm the results.

Dr. Shank also stated that nitrosamines have been known to exist for a long time. Several hundred people are known to have worked with propellants in which nitrosamines were present. If these people can be followed, there may be some epidemiological evidence that can be drawn. The exposure, however, will be difficult to gauge.

Dr. Shank cited the work of Dr. White (USDA) on the ingestion of nitrites. Dr. White reported that only 10 percent of the total dietary intake of nitrates, and 20 percent of the dietary intake of nitrites were derived from cured meats. The bulk of the nitrate comes from leafy vegetables, which is converted to nitrite in the saliva. Although the result of removing nitrite from meat would be small, evidence suggests that every effort should be made to reduce total nitrite intake.
Dr. Weisburger complimented Dr. Shank on the research. Some general comments from the Panel followed.

Dr. Weisburger asked about incidences in successive generations of rats and Dr. Shank reported that insofar as his work went there was no significant difference.

Dr. Edwards emphasized the significant role of nitrate conversion to nitrite in the mouth and the ingestion of nitrite from swallowing of saliva.

Dr. Keating remarked that there was a significant difference in the toxicity of nitrite alone to humans as compared to rats. Nitrite alone is toxic at relatively low levels in the human, while rats seemingly could ingest large amounts of nitrite without harm.

Dr. Wasserman asked whether all animals do not in fact show increased tumors when fed nitrosamines. He observed that all animals will react if the dose and type of nitrosamine is right. However, the only "in vivo" study in man was conducted on some ill people in 1968, and the protocol was questioned, so that results were inconclusive.

A new study by researchers is now in progress. In it, the researchers are actually eating nitrites and amines. To date, no nitrosation has taken place, although from a strictly chemical viewpoint, it should.

Dr. Wasserman reported on a study by the International Agency for Research on Cancer made in Iran where there is a high esophygeal cancer incidence. No nitrosamines were found in the diet but the study did not examine gastric contents.

Dr. Edwards called for additional research by USDA and FDA and Dr. Shaffner said that FDA was supporting research at MIT and elsewhere.

Dr. Mussman congratulated Drs. Shank and Newberne on their work. He went on to say that the gastric environment of man would probably never be exposed to the conditions which were studied in research animals. Whereas in animals a pure chemical relationship could be established in the stomach, in man there is a multiplicity of chemical reactions occurring at all times. There is competition for reactants under these conditions and even if chemicals such as those used in the Shank-Newberne study were introduced, it would be impossible to say they would behave in the same manner. In other words, it is extremely difficult to extrapolate from animal studies directly to the human.

Dr. Shank summarized the discussion by making the following points:

1. Nitrites plus secondary amines represent a hazard.

2. It is easier to regulate the amounts of nitrites in the diet than the amounts of amines.

3. Although the conversion mechanism exists in man, it is difficult to say whether conversion of nitrites plus amines to nitrosamines actually takes place in the stomach.

4. There is seemingly some epidemiological evidence in the China esophygeal cancer study.

5. Saliva is the single biggest contributor of nitrite to the diet.

6. The risks must be kept in perspective, including those arising from losing the anti-botulism effect of nitrite.

Dr. Mussman then asked for an update on the studies underway on bacon, country ham, and fermented sausages.

Dr. John Birdsall of the AMI reported that all the experimental bacon had been produced, first analyses were being completed and confirmatory work as needed would follow shortly. As soon as the work was completed the results would be forwarded to the Panel.

Mr. Oliver reported that the work on country ham hadn't started as yet because of lack of funds. Dr. Weisburger, upon discovery that the amount needed was only $10,000, sharply commented that the importance of the work was such that the amount needed was insignificant. Dr. Mussman also voiced concern.

Dr. Weisburger asked that Dr. Mussman report back to the Panel within a month on whether the study was proceeding so the Panel could decide whether further action was necessary.

Dr. Mussman then directed attention to the fermented sausage question. He acknowledged that to date most information had been offered by the Lebanon Bologna people, but asked Dr. Brown of the ABC Research Corp., to give a report on summer sausage.

The substance of Dr. Brown's report was that experimental packs of summer sausage were made with nitrite and nitrate, and with nitrite alone. In the chemical and organoleptic evaluation of the finished product, they were found to be completely comparable, and the Wisconsin processors were planning to remove nitrates from their products.

In replying to specific questions from the Panel, he reported a water activity of 0.87 to 0.92, with 0.90 to 0.92 being the usual range.

The nitrite level dropped quickly in the product, down to 20 ppm within a week. It was easier to control the nitrite level when nitrite alone was used. The salt content of the finished product was in the neighborhood of 3.0 percent. No residual nitrate determinations were made, but they will be studied in the near future.

Several pertinent comments were offered by members of the audience. One was that only half the permitted amount of nitrite was necessary in the production of fermented sausage. Another was that a company had been producing and marketing sliced Lebanon Bologna in Philadelphia for three years and had never used nitrate. The keeping quality was no problem, and the product was completely acceptable.

Dr. Wasserman reported that his laboratory made Lebanon Bologna, with nitrite alone, that was indistinguishable from the product usually made with 1700 ppm of nitrate. The residual nitrite was then lower because of lack of source (nitrate) for additional conversion. He had published a report on the work and had offered to work with the Lebanon Bologna Institute.

Dr. Mussman then reviewed the report previously submitted by the Lebanon Bologna Institute which in essence stated the product was safe and that without nitrate the product would be ruined. He stated that the December 1974 report was not acceptable as proof of need for nitrate, and the new study was also unacceptable. It was noted that among producers the use of nitrate varies all the way from zero to 1770 ppm of nitrate, and there is no agreement within industry as to nitrate need, either for microbiological safety or organoleptic satisfaction. The conclusion was that a residual nitrate level of 800 ppm or more, as indicated by the report, could not be justified.

The Executive Secretary mentioned that questions put to the Institute as to possible alternatives to nitrate, levels needed for safety, and problems resulting from its elimination had gone unanswered. He then asked the Panel for their thoughts on the subject.

The Panel offered the following:

Dr. Shaffner said that a new petition of that nature being made today would be denied. If the Lebanon Institute can't come up with better answers, data presented by others should be used.

Dr. Weisburger stated that if effectiveness of nitrate could not be demonstrated, it should be eliminated.

Dr. Albright, who did the work used as the basis of the Lebanon Institute report, stated that he didn't think the people who said that nitrite alone could get the job done, were correct.

Dr. Mussman summed up the discussion by saying that the new emphasis on nitrite and nitrate alone leads to a need for lowering of their intake in the diet and elimination where practical. The presence of a residual 800 ppm of nitrate was impossible to justify if only based on traditional processing methods. Eighteen months of the two year period given for obtaining answers to the specific problems relating to dry cured products and fermented sausages had gone by and he was deeply disappointed by the lack of progress.

Dr. Wasserman reported on preliminary work on controlling nitrite input by the use of immersion curing. To date, the preliminary production had been unsuccessful, showing uncured spots in the beef knuckles used. The new study will combine stitch pumping with immersion curing, and

monitoring of both pickle and product residual nitrite and nitrate levels at stated time intervals. Salt content will also be tested.

Dr. Mussman pointed out that one of the prime objectives of the study should be how much nitrite is going into the product. There is a need to define a system that will do this.

Dr. Mussman then asked Dr. Ivy, of the Monsanto Chemical Company, to present a report given to the Panel that day on the use of sorbic acid or polysorbate as preservatives.

Dr. Ivy said their work had just started and was in the nature of a preliminary investigation, but it gave indication that sorbic acid or polysorbate could be combined with decreased levels of nitrite to produce safety against botulism. The amount of sorbate used was in the range of 0.1 percent to 0.2 percent, lower than that presently allowed in cheese.

Replying to a question, Dr. Ivy said that they were working on a problem which surfaced in connection with the formation of mutagenic compounds when nitrites and sorbates were combined. Dr. Mussman suggested that the Panel carefully evaluate the report submitted by the Monsanto Chemical Comapny.

He briefly summarized the meeting, thanked the Panel and the audience, and closed with the suggestion that the next meeting be held in September or October of this year.

The Ninth Meeting - November 1976

The ninth meeting of the Secretary's Expert Panel on Nitrites, Nitrates, and Nitrosamines was convened at 9:30 a.m. on November 30, 1976, by Dr. Harry C. Mussman, the Executive Secretary. He introduced the members of the Panel to the audience and then asked if the Panel had any additions or corrections to the unofficial minutes of the eighth meeting held in April. None being offered, the minutes were accepted as official.

Dr. Mussman mentioned the possibility of increasing the size of the Panel in the future. He gave a brief summary of the events leading to the formation of the Panel and its objectives. He restated that the primary purpose of the meetings was to present all latest information and research for Panel discussion, but that substantive participation by the audience was encouraged.

Before going into the actual agenda of the meeting, Dr. Mussman advised the audience of the discussion at the eighth meeting concerning the continuation of the FDA-USDA working group which had been so effective over the past years, but which was in danger of being disbanded. He had received several letters, all strongly supporting continuation of the group, and forwarded them to the FDA; FDA has indicated they would keep the group together.

The first item on the agenda presented for discussion was a report by F. J. Ivey of Monsanto Industrial Chemicals Co., on some continuing work his group was doing on combining potassium sorbate with very low levels of nitrite in an effort to retain the organoleptic features of bacon and protection against botulism as well.

Dr. Ivey went into detail on the conduct of the research which had two aspects. One subject was the anti-botulism effect of sorbate. The other was an attempt to confirm the published work of Japanese scientists who reported on mutagenic effects associated with sorbic acid and sodium nitrite combinations.

In summarizing the conclusions reached, Dr. Ivey stated that bacon produced with 0.2 percent potassium sorbate and 40 ppm of sodium nitrite established an environment that was at least as inhibitory to Cl. botulinum toxin production as 120 ppm of sodium nitrite alone and organoleptically could not be found noticeably different by a consumer taste panel.

He also reported that they could not reproduce the mutagenicity results reported by the Japanese researchers. He then responded to questions by the Panel.

Dr. Greenberg stated that he hoped that Dr. Ivey was not saying that sufficient evidence had been produced for the panel to recommend adoption of the sorbate/nitrite combination as providing safety against botulism. He thought far more work would need to be done along with confirmation from different laboratories as well.

SORBATE RESEARCH

Dr. Ivey agreed but stated that in his opinion the work had shown a definite trend, and they were anxious to see what type of research would be needed by USDA for confirmation.

Dr. Keating questioned Dr. Ivey as to whether he had intended to leave the impression that the addition of sorbate had reduced the amount of nitrosamines present.

Dr. Ivey said no, what he meant to indicate was that a reduction in nitrite to 40 ppm was a factor that seemingly reduced the amount of nitrosamine formation in bacon. The Panel questioned this as a proper conclusion, since the number of tests (four) was much too small and the amounts of nitrosamines reported were well below the limits of confirmation. Dr. Ivey agreed and said in fact it would be straining to find a significant difference between 40 and 80 ppm of ingoing nitrite in terms of nitrosamines reported.

He was also questioned by Dr. Wasserman as to whether the mutagenicity tests were exactly the same as those run by the Japanese. Dr. Ivey reported that they were very similar, but admitted to some differences whose significance would be up to experts in the field to judge.

Dr. Edwards questioned Dr. Ivey about the finding that substitution of linoleic acid for sorbic acid did lead to some weakly positive findings of mutagenicity. She felt that since linoleic acid is an essential fatty acid widely distributed in food, it was important that the work be repeated because of the tremendous implications for (human) growth and development.

Dr. Schaffner, because of the nature of the work and questions by the panel, expressed the fear that it could be erroneously reported on and suggested the preparation of a much more detailed report and conclusions, answering the questions expressed by the panel. Dr. Ivey agreed that this would be in order.

Dr. Mussman emphasized that all nitrosamines reported were presumptive and could not actually be reported as nitrosamine findings.

Dr. Keating, in dialogue with Dr. Ivey, established that the mutagenicity reported was in all probability not due to nitrosamines, but rather to a reaction product of a lipid and nitrite, such as ethylnitrolic acid.

In answer to a question from the audience, Dr. Ivey reported that in their test they used 0, 40, 80, and 120 ppm of nitrite in combination with 0.1 and 0.2 percent sorbic acid.

Organic Nitrite Research

The next item on the agenda was a presentation by Dr. Rubin of Canada Packers on research performed on the use of organic nitrites in lieu of sodium and potassium nitrites as curing agents. Dr. Rubin advised that his discussion would be limited to the formation of two nitrosamines--dimethylinitrosamine and nitrosopyrrolidine in bacon. The work was done in collaboration with Unilever Laboratories, Colworth House, England.

After presenting tables showing various forms of organic nitrites (essentially alcohol esters of nitrite) in comparison with sodium nitrite, Dr. Rubin presented two conclusions--one, that some of the organic nitrites did a very satisfactory job of curing bacon so that organoleptically, it was not significantly different from that of cured with sodium nitrite; the other, that organic nitrite compared to inorganic nitrite showed little difference in terms of nitrosamine formation until isoascorbate was added. The organic nitrite results showed dramatic reduction in nitrosamine formation, but the inhibitory effect against botulism was lost, and therefore the work was not pursued.

Questions by the Panel brought out several significant points. Dr. Weisburger elicited the information that organic nitrites in themselves have health implications for the cardiovascular system since they are vasodilators. Dr. Rubin thought that organic nitrites would dissipate during cooking; in fact they hydrolize very rapidly in water (yielding alcohol and nitrous acid) which may explain why they show no improvement over inorganic nitrites unless isoascorbates or ascorbates are present.

Dr. Greenberg observed that a patent had been granted a British organization to use nitrous oxide for curing. His company had also done work in the field but found it too dangerous a substance to use in a food plant. He felt that butyl nitrite might be explosive, although Dr. Rubin disagreed on the point that it was any more hazardous than other organic substances now being used.

Dr. Wasserman pointed out that the methodology used, the Eisenbrand method, was accurate, but was known to produce an occasional false positive which made it necessary to confirm results by mass spectrometry. Dr. Rubin agreed.

Dr. Wasserman asked if organic nitrites gave positive results for nitrosamines by the method used. Dr. Rubin called upon his colleague,

Dr. Bharucha, who stated that under certain conditions they could, but their lab had developed cleanup procedures which separated the residual nitrites from nitrosamines.

Dr. Edwards, by questioning Dr. Rubin, placed emphasis on the fact that there were more nitrosamines present in the cooked-out fat than in the solid fried bacon. Since the fat is used for seasoning, especially in the South, this was another major concern that would warrant investigation as to linkage with certain types of cancer.

Dr. Keating asked about the necessity of using an emulsifier when curing with organic nitrite and whether the one used was an approved additive. Dr. Rubin replied that the one they used under lab conditions was readily available, there were many approved emulsifying agents, and one was necessary because of the insolubility of the nitrite esters in water.

Dr. Mussman questioned the use of 1,000 and 2,000 ppm of isoascorbate, in light of some of the earlier information given the panel which seemed to show that high levels of isoascorbate and ascorbate seem to stimulate growth of clostridia. Dr. Rubin ascribed the selection of 1,000 and 2,000 ppm to the differences between Canadian and U.S. regulations. Canada just states good commercial practice, and these seemed like nice round numbers. He stated that if additional work were done, they would probably use 1,000 ppm and abandon the 2,000 ppm.

Under further question, Dr. Rubin admitted that they were at a loss as to what further directions to pursue and were looking for help.

Cooperative Bacon Studies

Dr. Mussman then asked Dr. John Birdsall, scientific director of the American Meat Institute, to report on the bacon studies carried out cooperatively with the FDA and USDA in an effort to further reduce, and in fact eliminate, nitrosamines.

Dr. Birdsall presented the study parameters which called for each plant to produce 20 bellies, each of four different variables as follows:

Variable	ppm Nitrite	ppm erythorbate or ascorbate
1	0	0
2	40	550
3	80	550
4	120	500

The 20 bellies making up each variable were then randomly divided into four sets of five each and a 1-pound composite made from each.

Two of these composites were from the center portion of the belly and one each from the shoulder and flank.

This was done 3 weeks after the bacon had been prepared using the normal procedures of each plant other than the control of nitrite and ascorbate as shown in the protocol.

The bacon was fried at each plant at 340° F. for 3 minutes on each side, blotted with paper toweling and frozen for shipment to the laboratories.

After analysis, 25 samples of the 164 prepared were found to contain 5 ppb or more of nitrosopyrrolidine by gas chromatography, but only 10 of these could be positively confirmed by mass spectrometry. The highest amount confirmed was 9 ppb. One of the 10 confirmed was from variable No. 2; 4 were from variable No. 3; and 5 were from variable No. 4. In summary, it was stated that it was extremely difficult to get agreement between laboratories at the low levels of nitrosamines encountered, but the following conclusions were felt to be valid:

1. No samples were positive at a level of 10 ppb or more.

2. Lowering the level of ingoing nitrite from 120 ppb to 80 ppb did not seem to reduce the occurrence of low levels of nitrosopyrrolidine.

3. Processing variables existing between plants did not seem to affect the results.

The results of this study are summarized in the table at the end of these minutes.

Dr. Weisburger in questioning Dr. Birdsall elicited the information that in his belief, 5 ppb of nitrospyrrolidine was the present limit of technology in terms of ability to confirm results. Dr. Mussman remarked, however, that from statements made by Dr. Rubin and from advances in technology that were constantly occurring, it was highly possible that laboratories in the near future would be able to detect much smaller quantities. He raised the questions of learning how to deal with the significance of these very low amounts, perhaps even in parts per trillion.

Dr. Schaffner then stated that although the test batches showed a marked decrease in nitrosamines found, the FDA's continuing market basket monitoring had yet to come up with a negative sample, although the amounts of nitrosamines found had been lowered through the years. Dr. Birdsall replied that they, too, had been monitoring the market, and had identified some samples as being from plants which had voluntarily switched to the lower levels of nitrite and increased ascorbate recommended in the nitrite proposal. The analyses of those samples were in

close agreement with the barely detectable or nondetectable levels found in the controlled experiment.

Dr. Schaffner reiterated that their market basket was most likely to contain some samples from that type of production, yet were still found to be positive. He offered the thought that market abuse can lead to increased nitrosamine levels, and perhaps that was an explanation of the difference in findings.

Rulemaking Status

Dr. Mussman stated that USDA intends to get into such a monitoring program as well, but decided to wait until methodology had become more standardized and final rulemaking had been promulgated, making reduced levels of nitrite mandatory.

Dr. Mussman continued with an update on the status of the final rulemaking on nitrites and nitrates. Although the proposal was published in November 1975, and in April he had indicated imminent publication of rulemaking, he regretted making that statement in light of the unforeseen delays. At this point, the General Counsel is working on those questions needing his input, and when completed, the docket should then be ready for publication.

Methodology for Nitrosamines

Dr. Haggerty of the Midwest Research Institute then presented a statement dealing with methodology. He stated that reproducibility of analytical results depended upon many factors. Bacon in itself is a difficult product because of the many different chemical components naturally present and additionally produced as a result of the heat of frying.

Many different methods exist, all of which have merit; and though all methods have specificity, there are problems associated with the product being analyzed and method usage in various laboratories. Instrumentation not only varies from lab to lab, but even in day-to-day usage within a single laboratory.

One salient fact emerges. At this time, confirmation by mass spectrometry is a must before reporting a positive finding of nitrosamines, and such confirmation has been found to eliminate approximately 50 percent of the presumptive positives found by any of the other methods in common usage. By combining mass spectrometry confirmation with the gas chromatography method developed by FDA and reported in the Journal of the Association of Official Analytical Chemists, different labs could reproduce results as low as 5 ppb.

The thermal energy analyzer is one of the newer screening methods which gives promise of detection at much lower levels. Undoubtedly, other methodology will be developed which will further lower detection levels.

Country Ham Studies

The afternoon session was opened by Dr. Mussman informing the audience that the AMI had prepared a bibliography of over 900 entries dealing with the subject of nitrite and nitrosamines and that they had offered to make copies available to persons with a bona fide interest.

Dr. Weisburger then questioned the amount of residual nitrite that might be present in a ham when purchased by the consumer. The data indicated to him that the lot with 8 percent salt, 100 ppm nitrite, and 300 ppm nitrate would at this time seem to answer all questions satisfactorily. When Dr. Mussman asked if he wanted that entered as a recommendation by the panel, he answered that it would be best to await the nitrosamine analysis.

Dr. Haggarty stated that his laboratory was doing the work, and he expected it to be finished shortly. Dr. Mussman further found out that the remaining statistical work would be finished in early January, and noting the holiday season coming, asked that the full report be submitted by the end of January so that it could be resubmitted to the Panel for consideration prior to the next meeting, which he hoped to convene in early spring.

Dr. Schaffner requested industry reaction to the result of the study as well. Dr. Lechowich, in response to Dr. Mussman as to whether he would include recommendations as part of his study, pointed out that this was an experiment which dealt with only 50 hams. Dr. Mussman clarified his question by stating that he would expect industry to be in close contact with Dr. Lechowich, and if there were a discernable reaction on their part, asked that it be included in the report. Dr. Lechowich agreed.

Mr. Dudley, for the audience, reminded the Panel that the results of this experimental work concerned itself with only one kind of dry-cured product; there were many such products in production and it should not be deduced that what was applicable to dry-cured ham would be applicable to dried sausages. Dr. Mussman agreed that it was one of the larger categories and was being used as an indicator of what was possible in other products.

Dr. Keating asked for marketing patterns in that it would appear that in all instances, the 100 ppm nitrite and 300 ppm nitrite hams would have very modest levels of residual nitrite, especially if there was a storage period between finishing, distribution, and sale.

Further questioning brought out the information that the hams could be sold from 7 days on after finishing but that these were raw hams and were subjected to soaking, cooking, baking, frying, or a combination of those which could further change the residual nitrite present.

All variables considered, Dr. Mussman concluded that the panel would wait until the next meeting before deciding on further action regarding dry-cured hams. Panel members expressed some disagreement over the importance of nitrites as such and *in vivo* formation of nitrosamines--whether it could take place only in the stomach or further along in the intestinal tract as well.

He then introduced Dr. Richard Lechowich of Virginia Polytechnic Institute who presented a report on the work he had been doing on country hams.

Four different basic treatments were used in the study: Lot 1 - 8 percent salt, no nitrite or nitrate; Lot 2 - 8 percent salt and 150 ppm sodium nitrite, no nitrate; Lot 3 - 8 percent salt, 489 ppm nitrite, 1,700 ppm nitrate (normal commercial treatment); and Lot 4 - 8 percent salt, 100 ppm nitrite and 300 ppm nitrate.

Dr. Lechowich apologized for the fact that the data had not been statistically analyzed and some of the experimental work has yet to be finished, but did present the raw data and gave some general comments and references that seemingly will be supported by the study. The product is one which is processed by salt, nitrite and nitrate migrating to the center of relatively large masses of solid meat and fat after being applied to relatively small outer surfaces. To be acceptable, the curing and equalization times have to be of sufficient duration so that the product assumes those characteristics typical of country-cured hams and maintains keeping quality as well.

The times left in cure, aging, and drying are some of the variables. Others are the individual pieces of meat, different areas within the meat, size of the ham, temperatures maintained during the various processing steps, and the amounts of salt, nitrite and nitrate applied. Indications are that processing procedures will need further study and revision if changes are made in the use of nitrite and nitrate. On the other hand no toxin developed in any of the hams in any innoculation test yet completed, and a test panel indicated that Lots 3 and 4 seemed equally acceptable, Lot 2 less so, and Lot 1, the control least acceptable organoleptically.

Questioning by the panel brought out the additional fact that the salt concentration achieved, and in almost all cases the water activity measured, would be sufficient for preservation. Since the salt alone could do this, Dr. Weisburger, known for this aversion to high salt diets, questioned the necessity of any nitrate, and in fact nitrite. It was pointed out that there was variability within each ham and in some areas the brine concentration or the water activity might be considered of questionable safety factor. He also asked why reduced levels of salt and nitrite could not be pumped into the ham, therefore precluding the necessity a reservoirs of salt and nitrite in the dry-cure method.

It was pointed out that this was the normal method of producing regular smoked hams. Dry-cured hams depend upon the high salt for developing the characteristics which come to be known as country- (or dry-) cured ham.

Dr. Mussman summed up the situation, however, by saying he was sure he could speak for the Panel in saying that with the present state of knowledge, the Panel was in no position to disregard the importance of either the preformed nitrosamine or the possible combination of ingested nitrite or nitrate which ultimately might react in vivo with secondary or tertiary amines in the gastro-intestinal tract. The Panel is obliged to consider any steps toward reducing exposure to preformed nitrosamines and nitrate and nitrite to levels consistent with general safety considerations.

Fermented Sausage Studies

With no further questions, Dr. Mussman then introduced Mr. Warren Tauber, who was to report on the work being done by the Lebanon Bologna Institute on fermented sausages. These are representative of products which have traditionally been processed with larger amounts of nitrite and nitrate than were truly needed in order to provide an ongoing reservoir of nitrate during the long fermentation process. Dr. Mussman pointed out that the question of need for these large amounts has been repeatedly raised and hoped that at last some solid information would be forthcoming.

Mr. Tauber then presented a history of the traditional production of Lebanon Bologna, its acceptance, and its history for microbiological safety. He also presented the experiment presently underway which included production of three 400-pound batches: one, using normal, another with 1/2 the allowable nitrate, and another with 156 ppm of nitrite and nitrate.

These were stored for 1 month and then submitted to a taste panel which could distinguish between the three in triangle tests. This is now being repeated with product from only one company because of differences found between the four companies involved and because of costs and time involved. Data on the new test is not yet available.

Dr. Mussman then established that the levels referred to in the test were 1,700 ppm of nitrate as normal and 850 ppm nitrate for the half-rate batch. Under questioning it appeared that most analysis was directed at moisture, protein, fat, ash, salt, residual nitrate (average 887 ppm), residual nitrite (12 ppm average), and pH. Some little experimental work has been done using one third the legal limit of nitrate.

Under intense questioning from the Panel, the dissatisfaction with the work done by the Lebanon Bologna Institute was made evident. Salient points made were that the entire thrust of the work done was in the field of flavor and maintaining traditional production methods; in addition, taste panel methods were suspect, the protocol had not been submitted for acceptability prior to embarking on experimental work, and there was a continuing lack of response to the repeated demands of the Panel.

In summation, Dr. Mussman requested that results of the present experiment be in the hands of the Panel by February 1, and that Mr. Tauber meet with MPI officials and discuss a protocol that would be more acceptable in answering the needs of the Panel. If this were done, the Panel would decide by the time of the next meeting whether to extend additional time to the Institute or to recommend such other action as it deemed necessary.

Lebanon Bologna Studies by USDA-ARS

The next report was given by Dr. Smith of the USDA-ARS Eastern Regional Laboratory on the pilot plant production of Lebanon Bologna. Two different types were produced. One closely followed the traditional method which used 1,700 ppm of nitrate and depended upon the fermentation process to produce conditions conductive to the development of lactic acid which is a prominent flavoring agent in Lebanon Bologna. Micrococci are also present and reduce the nitrate and nitrite. The other was produced by using a starter culture rather than depending upon the natural development of the Micrococci and lactic acid bacteria. In this method, nitrite was used, no nitrate.

In each type, three mixtures were used--one with nitrite alone, one with nitrate alone, and one with a mixture of nitrite and nitrate. The conclusion reached was that there was no significant color difference nor any difference in the fermentation in any of the systems. Further experiments were conducted using nitrite at levels of 50 to 1,600 ppm, nitrate at those same levels, and no cure at all. In all cases normal fermentation, color, and flavor were produced until high levels of nitrite alone were used. These tended to inhibit fermentation. The part of the experiment which most drew the attention of the Panel was the apparent ability to produce a fermented sausage with low levels of nitrite alone, with very little residual nitrite, and with acceptable flavor. The point was made and agreed to by Dr. Smith that under the experimental conditions, it could not be said that Lebanon Bologna of typical flavor was produced. The next experiment would make use of a taste panel. The Panel congratulated Dr. Smith and his colleagues on a very worthwhile experiment and again pointed out to Mr. Tauber that that was the type of work which should have been carried out by the Institute and which might have been if the Panel had been given the opportunity to examine the protocol. Mr. Tauber agreed and said that he and Dr. Albright would contact program officials with designs for new experiments.

Concluding Discussion

That concluded the presentations listed on the agenda. Dr. Mussman asked if there was anyone in the audience who wished to make a statement. No one did, and Dr. Mussman then brought up the subject of bacon, noting that the 1 year which Agriculture stated was appropriate to review

processing changes had elapsed. He then asked the Panel to comment on the progress which they saw being made, especially from the studies reported on by Dr. Birdsall.

Dr. Weisburger, noting the lower levels of nitrosopyrrolidine reported, asked if the 125 ppm of nitrite and 550 ppm of ascorbate has been adopted by the entire industry. Dr. Birdsall stated that a limited survey indicated that those processors responsible for approximatley 75 percent of the 1 1/2 billion pounds of bacon produced annually, had gone to the proposed limits.

Dr. Weisburger then stated that everyone should be made to go to the proposed limits. Although he could not discount that trace amounts of nitrosamines might have some effect, in his view they were a very minor risk. He expressed his belief that we have reached a point that he was willing to live with for the present and would like to see more effort expended on what to him were more important disease considerations such as salt and hypertension, fat and cholesterol roles in health disease. He felt fat in bacon was more important as a health consideration than the nitrosamine levels reported in the study, and for his part he would be content to stop further experimentation for this time.

Dr. Mussman added that although Dr. Weisburger had not specifically mentioned the fact, he was probably considering the fact that the levels of nitrite being discussed struck a balance between the hazards from nitrosamines and botulism.

Dr. Wasserman agreed with Dr. Weisburger, except he did not agree that work should stop. Much research remains on how nitrosamines are formed and how the formation can be prevented. Also, actual production has to be proved, in addition to the highly controlled conditions of the experimental work. Dr. Weisburger agreed that experimentation should not stop.

Dr. Greenberg expressed the opinion that although the 125 ppm of nitrite and 550 ppm of ascorbate was satisfactory from a microbiological standpoint, further work such as was being done with sorbate and organic nitrite should not only be encouraged but insisted upon.

Dr. Schaffner asked the Department to take cognizance of the fact that there were no tolerances set for nitrosamines and that if monitoring turned up violations, prompt action should be taken to see that the manufacturers were maintaining proper controls.

Dr. Edwards agreed and said that she would like to see other types of research conducted to determine possible ingestion patterns and their relation to types of cancer and cancer incidence.

Dr. Mussman made the analogy that research was like working toward opening a door, only to find that to open the door you had to open several others which opened more passages worthy of investigation. He did not want to leave the impression that there was an interminable process ahead, but rather to advise those who felt that the wheels were turning too slowly that the work was of a nature that could not be done overnight.

The other point was that he did not believe he heard an actual recommendation from the Panel. He believed that Dr. Weisburger and the others had said that the Panel, in considering the state of the art, did not believe that they were ready to make recommendations beyond those contained in the proposal. He did feel, however, that some information should be disseminated to the world to let people know the progress which had been made and which had led to the decisions and recommendations of the Panel.

Discussion amongst the Panel then became general as to how best to accomplish this. It was decided that a short paper would be prepared by the program, giving a review of the Panel's activities since its formation. This would be circulated to the Panel for such changes as they thought appropriate. The paper would be ready in final form for issuance by the time of the next meeting.

Dr. Mussman assigned Mr. Fried the task of assembling the position paper. He noted, too, that it was especially important that this be done in view of the worldwide interest in the subject and the number of people who were critical of the pace at which decisions were being reached. No further comments being made, the meeting was closed at 4 p.m.

Nitrite levels ppm	0	40	80	120	Total
Samples tested	38	39	38	39	154
GLC +5 ppb NPy	1	3	9	12	25
A	0	0	0	3	3
B	0	1	2	1	4
C	0	0	2	1	3
D	1	2	4	5	12
E	0	0	1	2	3
Res. No2 ppm	3	9	15	20	
Res. Eryth. ppm	0	286	264	232	

A = Samples confirmed by GC-MS at two or more laboratories.
B = Samples confirmed by GC-MS at one laboratory but not confirmed at another laboratory.
C = Samples confirmed by GC-MS at one laboratory but not tested at any one laboratory.
D = Samples which could not be confirmed.
E = Samples which were depleted or lost so that confirmation could not be attempted.

The Tenth Meeting - March 1977

Dr. Mussman convened the 10th meeting of the Secretary's Expert Panel on Nitrites, Nitrates, and Nitrosamines at 9:30 a.m. on March 29. The minutes of the ninth meeting were accepted without correction. Dr. Mussman told the audience that he expected Mrs. Carol T. Foreman, the newly appointed Assistant Secretary for Food Safety and Quality Service, to spend some time at the meeting. He then gave a brief history of the previous meetings, and reviewed the day's agenda.

POSITION PAPER

Dr. Mussman said that the Panel had been given a copy of a proposed position paper that morning. He asked that the audience not request copies until the Panel had been given time to edit and comment on the proposed paper. He then introduced Dr. John Birdsall of the AMI.

BACON STUDIES

Dr. Birdsall referenced the inplant bacon study which had been reported on at the previous meeting. As a parallel to that study, retail bacon samples were collected and analyzed for nitrosamines after frying. Forty eight samples were collected from six locations throughout the country. The date of purchase, brand name, establishment number, "sell-by date," ingredients, and frying dates are recorded for each sample. At the time of frying, residual nitrite, nitrate, and ascorbate analyses were made. Twenty-six different manufacturers were represented in the sample. Each firm was asked about the concentrations of nitrite, nitrate, and ascorbate used in that particular pack. This will permit comparisons to be made between bacon produced according to the Panel recommendations (125 ppm of nitrite and 550 ppm of ascorbate or iso-ascorbate) and bacon produced with different levels.

Twenty-seven analyses have been completed at one laboratory. No confirmatory checks by other labs have been made as yet. Birdsall reported that on the basis of the preliminary analyses, bacon from producers using the 125 nitrite/550 ascorbate cure showed results essentially similar to the plant study. Higher nitrite or lower ascorbate invariably resulted in positive nitrosamine findings. This will be an ongoing study.

Residual nitrite data are also being accumulated for cured products at various intervals after production. Work done by Jonathan White (USDA) has indicated an average residual value of 52 ppm. Thought is that most residuals are done by USDA within a day or two of production. The consumer normally eats the product 2 weeks or more after production, and in some cases, much later.

The data obtained will be for residual nitrite levels at intervals of 1 week, starting at week one and going for at least 9 weeks. There is a rapid drop during the first few weeks. Preliminary data suggests a drop from the 52 ppm average reported by Dr. White to 20 ppm. More detailed reports will be available within a few months.

Other studies being conducted are means of blocking nitrosopyrrolidine formation by the use of alpha-tocopherol (Vitamin E) and other nitrosation blocking systems. To this end a corps of organic chemists has been assembled. Rapid screening methods to aid in running larger numbers of samples are also being examined.

Q. Mrs. Zawell - Are there figures on differing consumption levels of nitrite in given populations?

A. Dr. Birdsall - Very little in the United States and those figures are old (1965). There are some known high exposure levels in Columbia, and that population is being studied to determine if there is an epidemiological relationship between the high nitrite intake and cancer incidence.

Mrs. Zawell - In China, too, I believe. Also, how about low income people with diets heavy in cured meats, greens, etc.

Dr. Birdsall - I do not know of any, but there are two studies on high cured meat levels to rats (approximately 40 percent) showing no excess tumor formation over control groups. The cured meats in the diet had an extra 1,500 to 5,000 ppm to nitrite added as well.

Dr. White thinks that epidemiological studies would be very appropriate. He also asked who was doing the residual nitrite studies and was informed that individual companies were doing them. Alpha-tocopherol as a blocking agent had also been under study in his lab and was found to have an effect, especially in the presence of ascorbate.

Dr. Keating asked about budgeting for the work. Dr. Birdsall reported that his budget for the year was $75,000 but that did not include the money being spent by industry.

Dr. Mussman then asked Dr. Schaffner for an update on FDA's latest figures on market basket findings of nitrosamines in cured meats.

FDA Market Basket Study of Cured Meats

Dr. Schaffner presented an FDA report on the latest findings of nitrosamines in samples of cured meats procured in the marketplace. All samples of cured meats were negative except for bacon. All raw bacon was negative, but nine of ten fried samples showed amounts of nitrosopyrrolidine ranging from 5 to 25 parts per billion (ppb).

These were confirmed by mass spectrometry. A discussion followed in which the question was raised as to whether the samples tested were being produced under the present regulations or whether the amount of nitrite had been reduced to 125 ppm and ascorbate used at the 550 ppm level. Dr. Schaffner said the codes of the packages were available, and it was agreed that USDA would check the processes to determine what levels of nitrite and ascorbate were being used.

The Panel then discussed the problems posed by the continued findings of nitrosamines in bacon. Emerging from that portion of the session were requests to check on demographic distribution of cancer in the United States; continue with the effort to determine actual risk posed by the amount of nitrosamines present in bacon; and require industry to immediately institute the 125 ppm nitrite and 550 ppm ascorbate pickle formulation.

Residual Nitrite

Dr. Engel (USDA) then reported on comparison data put together from laboratory analyses of samples submitted for residual nitrite. The years covered were 1971, 1975, and 1976. The trend, although statistically questionable as to significance, was upward; that is, increased residual nitrite. Dr. Engel had no explanation for this since the graphs were prepared from accumulated data rather than from an experimental design. Possible explanations offered were decreased turnaround lab time, and sample delivery time. Since residual nitrite dissipates quickly at first, faster analysis can account for higher results. With the known decrease in the use of nitrate and lower amounts of ingoing nitrite, there is expectation of lower residual levels.

Country Ham Study

Dr. Lechowich then gave a final report on the country ham study which had been in progress. He summarized the findings by stating that under the experimental conditions of the study, commercially acceptable country hams with microbiological stability could be produced using curing mixtures applied at the rate of 8 percent salt plus 1,700 ppm of sodium nitrate and 490 ppm of sodium nitrite. Eight percent salt and 300 ppm of nitrate and 100 ppm of nitrite was also satisfactory. The best test panel score went to the latter. Dr. Lechowich went on to talk about the wide variability in penetration of salt and nitrite into the ham and therefore the need for nitrate as a reservoir. Although hams of somewhat lower quality were produced with salt and nitrite alone, there was a greater percent of spoilage in that test lot. For these reasons, he felt that although further experimental work could be done with lowered amounts of nitrite and nitrate, the 100 ppm nitrite and 300 ppm nitrate were approaching the lowest limits. This was especially true since the study found no confirmable nitrosamines when the hams were fried. He went on to say that by the time of sale the residual levels

of nitrite and nitrate, even from the highest input lots, were at the low level of 10 ppm.

He advised going slowly before recommending further reductions. He also quoted a letter from Dan Lawrence, Executive Director of the North Carolina Meat Packers Association, which said that members of that association were using the 100 ppm nitrite and 300 ppm nitrate on a commercial basis.

The Panel was pleased to hear that commercial production was going on, and the recommendation was made that USDA do what was necessary to implement the 100/300 ppm levels. The members expressed satisfaction with the study, and although some felt that further experimentation should go on to possibly lower the ingoing amounts, the main body felt that the 100/300 ppm levels were a satisfactory solution to the problem of nitrosamine formation, while minimizing the ingestion of nitrite as such.

Labeling

The question was asked if some form of labeling could be used to denote hazards. Dr. Mussman replied that anything was possible in the way of labeling providing that it was truthful. The Panel was divided on the necessity and usefulness of such labeling. Dr. Mussman pointed out that although many options in labeling were available it was desirable to supply as many consumers as possible with enough information so that they could make the choice of the type of labeling which would be most informative. During the discussion, emphasis was placed on the potential abuse of dry-cured products. Questions were raised about the necessity for handling instructions on labels. Country hams were stated to be so safe as to make such instructions superfluous, but the discussion spread to meat products in general.

Dr. Mussman said that from a personal viewpoint he preferred products that were safe and required no special handling instructions. Various panelists quoted from surveys which showed the difficulty of maintaining proper storage conditions strictly by instructions on the label.

The discussion concluded with the Panel recommending that the 100 ppm nitrite, 300 ppm nitrate formula be adopted officially and that more research be conducted to determine the feasibility of further reducing those levels.

Dr. Mussman then asked Dr. Ivey of Monsanto Chemical for a report on their research into the use of potassium sorbate as a preservative.

Other Chemical Preservatives - Potassium Sorbate

Dr. Ivey reported that he had given the Panel copies of a protocol for new research on the use of potassium sorbate as an inhibitor of Clostridium botulinum. The protocol had been previously discussed with USDA and he reported on it to the group. Bacon was to be treated with two levels of potassium sorbate in combination with 0, 40, 80, and 120 ppm of sodium nitrite. In addition, sodium ascorbate at 550 ppm was to be used when nitrite was used. An inoculum of 3,500 spores was to be used and packages were then to be opened and tested for toxin production at regular intervals. The test product was to be held at 13 degrees Celsius, but in addition, some were to be held under abuse conditions, 27 degrees Celsius, and the final tests were to be performed when all packages were observed to be spoiled. These tests would further the research previously done and reported by Dr. Ivey.

The Panel felt that the design was good and should go a long way toward proving the efficacy of potassium sorbate. Additional work would be done on residual sorbate, nitrite, phosphates, pH, and nitrosamine formation. The USDA would confirm results on separate samples.

Botulism Survey

At the close of the presentation, a request was made by the Panel that several leaders in the field of botulism study be assembled and make a review of botulism for their benefit at the next Panel meeting. Dr. Mussman agreed to attempt to assemble the group.

Semi-Dry Sausage

Dr. R. B. Sleeth of Armour made the next presentation which concerned itself with an overview of the production of sausage. The history of sausage dates back to long before the birth of Christ. There are various types, ranging from the fresh, uncured sausages, such as breakfast sausage; to the cooked sausages such as frankfurters, to the semi-dry and dry sausages. The semi-dry sausages are generally fermented, may be fully cooked, and are only dried during the fermenting, cooking cycle. Production can last from 1 to more than 10 days. Dried sausages are fermented and dried for as long as 120 days and lose 25 to 40 percent of their weight.

Dr. Sleeth emphasized the tremendous variety and complexity of these products. He reiterated that to a large extent production of these sausages remained an art rather than a science. This pointed up the importance of nitrite and in some cases nitrate (as a reservoir of nitrite) to maintain safety until the final sausage was produced.

As an adjunct to that report, Mr. Fried presented some data indicating the number of semi-dry and dry-cured sausages now being produced without

nitrate. Nitrate was traditionally used as a reservoir for nitrite until safety of product was assured by a combination of salt, pH, and mositure/ protein ratio in the finished product. Indications were that many establishments had eliminated nitrate from their formulation, but Dr. Mussman noted that tradition was hard to overcome and it would take some time to see if nitrate could be eliminated entirely. A question concerning Lebanon bologna has held pending the next presentation which was by the Lebanon Bologna Institute.

Lebanon Bologna

The presentation by the Institute followed closely those presented at earlier meetings and previously reported. The Panel had the same objections to the basic presentation and direction of the Institute. They felt the protocol was inadequate and in the nature of foot-dragging.

Mr. Fouche', as a member of the Institute, did say, however, that experimental results would be available to the Panel at the next meeting and all haste would be made to give the Panel the research it needed to make a recommendation.

Dr. Mussman agreed that the Panel would wait until the next meeting at which time a recommendation would be forthcoming.

Chemical Preservatives - Parabens

Dr. Astill of the Eastman Kodak Company then asked permission to present a paper on the use of a class of chemicals which showed promise as a substitute for nitrite. The chemicals were propyl and methyl paraben, and work at the University of Wisconsin indicated that levels of .05 percent each day they would provide botulinum control equal to that of 60 ppm of sodium nitrite.

In answer to questions, Dr. Astill responded that there were some figures available to show comparison with amounts of nitrite other than 60 ppm. He gave indications of the need for coloring the product, adding antioxidants, and that the parabens had GRAS status. Dr. Mussman indicated the interest of the Panel in nitrite replacements and was pleased to hear that Dr. Astill would contact the Department shortly to further the work needed for acceptance.

There being no further comments or discussion, the meeting was adjourned at 4 p.m.

The Eleventh Meeting - May 1977

Dr. Mussman convened the 11th meeting of the Secretary's Expert Panel on Nitrites, Nitrates, and Nitrosamines at 9:45 a.m. on May 31, 1977. He then introduced the Panel members, some of whom were newly appointed or appearing for the first time. The complete Panel now consists of Ms. Carol Tucker Foreman, Assistant Secretary of Agriculture, Chairperson, Dr. Harry C. Mussman, Acting Associate Administrator, FSQS, Executive Secretary; Drs. Edwards, Greenberg, Keating, Wasserman, Schaffner, Lijinsky, Jacobson, Mirvish, and Falk; Ms. Ellen Zawel, and Ms. Sundberg-Werner. Ms. Sundberg-Werner of the University of Wisconsin-Stout was appearing at her first meeting as were newly appointed members, William Lijinsky, Frederick Cancer Research Center; Michael Jacobson, Center of Science in the Public Interest; Sidney S. Mirvish, University of Nebraska; and Hans Ludwig Falk, National Institute of Environmental Health Sciences.

Ms. Foreman then addressed the Panel. She said that President Carter urged the elimination of as many advisory committees as possible. The Panel's charter expires on September 21, and she hoped that it could complete its work by then. Toward this end, she has added some new members and asked the Panel to meet monthly rather than quarterly. The subject of discussion for this meeting was primarily botulism and the role of nitrite in its prevention. Subsequent meetings would deal with the potential carcinogenic effects on nitrites, nitrates, and nitrosamines and then a discussion of an outline for a final report.

Dr. Mussman then introduced Dr. Gene Gangarosa of the Center for Disease Control at Atlanta, Georgia; Dr. Charles Duncan of the University of Wisconsin; and Mr. Ralph Johnston of the Meat and Poultry Inspection, USDA, to discuss botulism as requested by the Panel at its 10th meeting.

BOTULISM

Dr. Gangarosa spoke first and addressed the following subjects:

Aspects of the Disease

Botulism was first described in Germany, and the term derives from the Greek word for sausage. Botulism is not common, but very serious when it occurs--often resulting in death. Most agree it is an intoxication, although new evidence indicates it may also result from infection with the organism and production of the toxin in man. A food intoxication remains the basic definition, however. The toxin affects the nerves responsible for the respiratory muscles, and this impairs the respiratory function.

Nature of Organism

C. botulinum is remarkably adaptive. It produces spores which can survive for remarkably long periods of time, essentially in a state of suspended animation. The spores are very heat resistant, although the vegetative cells and the toxin are not.

Incidence and Geographic Distribution

In the United States botulism occurs mainly on the west coast. There have been a total of 700 outbreaks in the seven decades of this century--an average of 10 per year although there have been slightly more than this in the past 2 years.

Toxin Types

There are three main toxin types: "A," which accounts for two-thirds of all outbreaks and predominates on the west coast; "B," predominant on the east coast, particularly in the northeast; and "E," focused in Alaska and the Great Lakes.

Treatment

Whereas early administration of antitoxin is usually thought of as the primary treatment, early intensive treatment in a facility with provisions for optimum care of respiratory complications is best. Death to case ratios have decreased from 40 or 50 percent to about 30 percent and this intensive treatment is probably responsible. Older people are most susceptible, although the exact reason is not known.

Types of Food Involved

In most cases over the 7-decade period, the vehicle of transmission was undetermined. Of the approximately 22 percent which were identified, vegetables accounted for approximately 20 percent, and beef, poultry, and pork together, for 2 percent.

Other Types of Botulism

Wound botulism occurs when contamination of a wound with C. botulinum results in growth and toxin formation; this is a process similar to tetanus.

Infant botulism appears in the first few months of life. The ingestion of spores in all probability leads to growth of the organism and toxin production in the intestinal tract.

Dr. Duncan then addressed the following subjects with particular emphasis on the hazards associated with C. botulinum:

Recognized Types of Toxins

Dr. Duncan presented a table showing the now recognized types of toxins A, B, C, C alpha, D, E, F, and G and the toxigenic types of C. botulinum which produced them.

Interestingly, a strain can gain and lose toxigenicity, rather than remaining constant.

Occurrence and Geographic Distribution

This was a more detailed picture than that given by Dr. Gangarosa, with a study of Russia presented in addition to the United States. The organism is ubiquitous in soil throughout the world, as well as in mammal, bird, and fish intestines. About 10 percent of all soil samples are positive for botulinum isolates. The relationships of C. botulinum to putrefactive anaerobic organisms were pointed out. They were similar and are found together. Indeed, the putrefactive anaerobes are frequently used as indicators of the possibility of botulinum being present. Some heat preservation systems are based upon killing the spores of one of the putrefactive organisms.

A study of semipreserved meats showed that although most were negative for botulism, 5 of 100 samples of ham were positive, and smoked turkey was also found positive. Putrefactive anaerobic spores were present in meats in much higher precentages, and again Dr. Duncan emphasized that where they occur, C. botulinum can also be found. He also pointed out that some organisms, such as C. perfringens, could inhibit C. botulinum so that the possibility of false negatives exists in isolation studies.

Controlling Growth and Toxin Production

1. Low Temperature - Low temperatures are one of the basic means of controlling microbial growth. C. botulinum types vary in their ability to grow at low temperatures. Type E has shown the ability to produce toxin at 3.3¼ C.; and Type F at 4¼ C., well below refrigeration temperatures. Variations in strains of the same type also vary in their ability to produce toxin at different temperatures. This factor, combined with the distinct possibility of temperature abuse, makes it hazardous to use low temperature alone as a control.

2. High Temperature - The spores of the same type, and different strains of the same type, vary in their ability to withstand heat treatments. Spores of Type A have been found to be among the most heat

resistant spores known. Spores can be injured by heat, however, and become more susceptible to the other controlling factors.

3. Disinfectants - C. botulinum is more susceptible to chlorine than are spores of aerobic organisms. Chlorine effectiveness is dependent upon proper pH.

4. Spore Load - The effectiveness of various treatments is dependent upon spore load. What is effective at the normally low load present can break down and not function if the spore load is increased to a large extent. One viable spore, given the right conditions, can grow and cause toxin production. Therefore, controls must be set for complete inhibition.

5. Salt - The concentration of salt in the product is a definite factor, although for complete control it is necessary to go far beyond the limits of organoleptic acceptance.

6. Nitrite Concentration - This has a known, attested effect in controlling C. botulinum. The question remains as to how low the concentrations may go, and to what extent other factors must be controlled in order to provide continued safety against botulism. A change of parameters in any of the conditions may force a change in the others in order to maintain safety.

7. Ph - The acidity of the environment plays several different roles, but probably the most important is its effect upon nitrite. A low pH is needed so that nitrite when present is converted to nitrous acid, which appears to be the active inhibiting agent in controlling spore germination.

Postulated Role of Nitrite

1. Enhancement of spore destruction by heat.

2. Increased rate of spore germination with subsequent heat killing of the germinated spore.

3. Inhibition of spore germination.

4. Inhibition of growth of germinated spores.

5. Reaction with other components to form an antimicrobial compound in meats.

The only positive conclusion is that number four is one of the factors involved. Although there is existing evidence, both positive and negative, on the others, more research is needed.

Botulism is Hazardous When:

1. Viable cells or spores are present in food.

2. The composition of the food allows growth and toxin formation.

3. The food is held for a suitable time at a proper temperature for growth and toxin formation.

4. The food is eaten uncooked, or without proper heating.

In conclusion, Dr. Duncan pointed out that C. botulinum is present in the meat supply and warned against changing the known safety of the present preservation system without being equally sure of the safety of the new system.

Mr. Johnston then briefly added some comments pertinent to the present-day production of meat products.

Mass production, coupled with mass distribution, means a greater potential for large outbreaks. New products and more formulated products mean that spores are present naturally from meat itself, as well as from dried milk, cereal, soy, onions, olives, pimientos, and spices from all over the world. Most of these are ground crops, and they carry spores from the soil in which they were grown. Fish and fish proteins will undoubtedly be used in combination with meats.

C. botulinum grows best in meat products which have been cooked, smoked, or lightly salted in such a manner as to destroy most of the common spoilage bacteria. Temperature abuse of the finished product must then occur. Unfortunately, cured meats, because of their safe history, are rather routinely subjected to temperature abuse. This is so well known, that uncured products are not permitted to be canned, pasteurized, and labeled "Keep Refrigerated."

Some meat products, as part of the process, are intentionally heat-abused at the processing plant. Country hams and fermented sausages are examples. They are held for extended periods of time at 75 to 95 degrees F. in order to allow development of typical flavor. It is essential for an antibotulinum factor to be present if we are to continue to have these products.

Dr. Mussman then pointed out that the presentation on botulism was at the request of the preceding Panel. He stated that although Dr. Duncan's and Mr. Johnston's presentations sounded like a testimonial to the use of nitrite, they were in reality a recognition of how the problem of botulism had been dealt with over the years. The fact is that nitrite,

in the laboratory and in the marketplace, has an inhibitory effect on clostridia. From here, the Panel will be considering alternative methods of preservation which might be substituted for nitrite if it were significantly reduced.

Dr. Mussman then asked Drs. Duncan and Gangarosa and Mr. Johnston to answer questions from the Panel.

----- Questions by Dr. Lijinsky -- Can the use of nitrite be avoided by the use of high heat? High heat would ruin the organoleptic acceptability of canned products such as ham and luncheon meat. They would turn to mush.

Is that true of bacon? No, because bacon is a refrigerated product, one of those that during processing is heated just enough to kill off competing organisms.

Why not avoid vacuum packaging? You can get clostridia growth in a package which is not vacuum packaged. Anaerobic conditions, suitable for growth, exist within a few millimeters of the surface.

Then why not put nitrite in fresh meat? Consumers do not expect it. They know it must be carefully handled, and competing spoilage organisms would make the meat unfit to eat, so that the danger from botulism is practically nonexistent.

----- Questions by Dr. Mirvish -- Is it the ingestion of the toxin which is the danger, not eating the bacteria? Yes, but there are know cases of infant botulism arising from ingestion of the organism with colonization and toxin production in the intestine.

Should not more work be done on the exact mechanism by which nitrite works? Yes. The nitrite seems to inhibit after it has been converted to nitrous acid, but the exact mode or modes of action are unclear.

Is nitrite more effective on some organisms than others? Not necessarily.

Can the organism be inhibited by acid in the adult and not in the infant? Perhaps, although not enough is know to state positively.

----- Questions by Ms. Zawel -- Can it be that some of the social changes taking place may be responsible for infant botulism? Should we be looking at things other than food? The exposure is clearly not a food in many instances. No doubt the problem in infants is quite different.

Could I get a picture of the correlation between food-borne botulism and the incidence of botulism in general? Dr. Gangarosa expressed the thought that wound and infant botulism were beyond the purview of the Panel.

----- Questions by Dr. Wasserman -- Was not there a paper summarizing a number of botulism cases in France? Yes, and the products were homemade, inadequately salt-cured hams.

----- Questions by Dr. Jacobson -- Have there been any cases of botulism associated with commercial nitrite-free frankfurters or other sausages and bacon? Dr. Gangarosa said he was 99.9 percent sure that there were none. Mr. Johnston said there was one case due to home-prepared venison jerky with cure.

Since botulinum can get into meat from fecal material, hair, spices, etc., could cleaner plants reduce the incidence of spores in meat? Mr. Johnston said, "No, the washing procedures are better than they have ever been. There certainly will always be room for improvement, but the problems associated with spill crops are such that it seems like an impossible task to eliminate spores."

Has a comparison been made between the cleanest plants and the average plant from the standpoint of botulism? Mr. Johnston answered, "No, we have accepted the fact that the organism is present and our procedures are designed to control it.

Some plants making nitrite-free hotdogs take great care to reduce microbiological contamination. Nitrite need might be reduced if all plants took that care." Mr. Johnston replied, "I would not want to assure any packer that the nitrite-free product did not contain some degree of risk from C. botulinum."

Since the effectiveness of nitrite varies with pH, is the pH of meat optimal for nitrite effectiveness or would it be reasonable to modify the pH slightly to reduce the need for nitrite? Dr. Duncan replied, "Meat falls in the pH range of 5.5 to 6.3. As the pH is dropped, the effectiveness of the nitrite is increased."

If you add vinegar to Spam it might reduce the need for nitrite. Dr. Duncan replied, "I suppose, if you like vinegar and Spam."

Does the amount of nitrite needed vary with the number of spores per gram? "Yes," was Dr. Duncan's reply.

Most studies seem to use inocula of 100, 1,000, or 10,000 spores per gram and those studies indicate 150 to 200 ppm of nitrite are needed for inhibition. Since the average load was stated as one spore per 15 pounds of meat, could not the nitrite amount be lowered? Dr. Duncan answered, "I think the point is well taken, although we do not know very much about it. We know what is needed for the levels we were working with. How much the nitrite can be lowered, and still maintain protection even against low numbers, cannot be answered. The basic principle in the expermimental work has been the same as that used with testing

carcinogenicity. You do not use a low level. You use a load that gives results and then extrapolate back. I have not seen extrapolation back through." Dr. Duncan answered, "It has been done. In the work of Hans Riemann at the University of California, it was shown that if vegetables with a realistic load of spores needed a 12 D cook (expression of numbers of minutes at certain temperature needed to reduce spores load by 90 percent), then meat is only given a 4 D cook because of the lower incidence of spores expected. And here, there is not only the heat, but inhibitory effect of salt and nitrite as well."

Dr. Jacobson said that he would still like to see a simple graph showing nitrite needed versus various spore loads. Dr. Greenberg pointed out that the degree of safety being given by heat to canned meats was only 1/100 of that given to vegetables--the reason being other inhibitory factors present--salt and nitrite.

Dr. Wasserman expressed the thought that he was against the overkill type of experiment, whether testing botulism protection or carcinogenicity. Storage for toxin production went as long as 6 months at 80¼ F.; and he wondered whether that was realistic (whether any product would be kept that long). The definitive answer was from Dr. Keating, who said that anyone who had been in Vietnam or the second World War and had eaten canned corned beef should answer that question affirmatively.

Dr. Keating pointed out that infant botulism is rarely considered in a actual occurrence of the disease and is in all probability limited because of local health department reporing methods. Dr. Gangarosa supported this statement.

Dr. Edwards then questioned the possibility of botulism through infection causing the death of children who became dirt or clay eaters. She wondered whether any information had been gathered on that point. Dr. Gangarosa was not aware of any, but theorized that since infant botulism only affected very young infants, they would probably have developed immunity by the time they started eating dirt.

Ms. Zalel asked if most botulism came from home-canned foods, mostly vegetables? Upon receiving a "yes", about 90 percent answer, she then asked what, if any, epidemiological work had been done on the relationship of carcinogenicity and nitrites ingested from sources other than meat. Dr. Gangarosa said he was not aware of any.

Dr. Falk then elaborated on Ms. Zawel's questions. He asked if a balance sheet were available for nitrite since some could combine with amines to form nitrosamines, some could combine with proteins of the hemoglobin type, some went into nitrous acid which inhibited botulism, and some were unaccounted for. He felt that all of these primary reactions made an almost impossible task to define how much was needed for one spore inhibition. And since so much nitrate was available from the

total environment, a totally different type of balance sheet was needed. Dr. Duncan said that the amount ingested from other sources had been presented to the Panel by Dr. White.

Dr. Mussman interpreted the previous question in a different manner. He had heard the question as, "If nitrate reacts with so many different things, then we know that some goes this way and some that, and we cannot pinpoint exactly what went in each direction. How then can one arrive at a finite figure as to the minimum needed for control of the hazard? Certainly such a figure is presently unavailable."

Ms. Zawel asked if the nitrite protection disappeared as the residual nitrite disappeared? Dr. Greenberg answered that the general belief was that it was not the residual that was important but the amount available to the spore at the time it was in a position to grow, which generally meant at the time the product was manufactured.

Dr. Jacobson then asked if it were true that botulinum could not grow without water? The less water, the less it is able to grow. In general, Dr. Jacobson was making the point that each water reduction step decreased the ability of the organism to grow and therefore would require less nitrite for inhibition. He used frankfurters as an example. The answer he received from Mr. Johnston was that although that was true to a limited extent, botulinum grew very well as the water activity of fresh meat which was about 0.985, and even the addition of salt and nitrite did not decrease the water activity enough to prevent growth.

The water activity figure given for botulinum control was 0.93.

To clarify the discussion, Dr. Mussman pointed out that as you come down the scale from 1:0, in terms of relative humidity, to 0.9, 0.8, 0.7, etc., a point is reached where various organisms cannot grow, and 0.93 is the level for C. botulinum.

Dr. Lijinsky asked if the botulinum spore level was equal for all meats, and why some were canned with nitrite and some without? The answer given was that the acceptability of the product to the consumer was the determining factor. Chicken, for example, is traditionally eaten well cooked, so it is retorted without nitrite, and in a process which would probably ruin the acceptance of luncheon meat.

Dr. Mussman then summed up by saying that the morning session had shown that botulism is a predictable hazard which, although occurring infrequently, is nevertheless present. It is of such a public health significance that no one wishes to fool around with it as a potential hazard. Nitrite over the years has functioned to inhibit the outgrowth of C. botulinum in combination with a variety of other mechanisms in a way not completely understood.

Dr. Mussman opened the afternoon session by mentioning that each of the Panel members had a copy of a letter from Ms. Foreman to Dr. Donald Kennedy of the Food and Drug Administration spelling out the Department's position regarding the use of nitrite and nitrate in poultry. It stated that upon due consideration it was left to FDA for jurisdiction as to whether or not nitrite and nitrate are color additives or food additives in poultry. After they make that determination, the Department will take followup action.

He then indicated that the next topic would be whether alternate methods of preservation such as heating, freezing, etc., could be used to eliminate the hazard of botulism, and whether by using one or a combination of such methods, perhaps combined with greatly lowered amounts of nitrite, the traditional character of the product could be maintained. Before doing that, however, he read the position paper which the Panel had prepared to summarize the findings of the first ten meetings. He emphasized that he was taking the time to read the paper because it did provide a jumping off space from which the Panel would then take a new direction for the remainder of the meetings. A copy of that paper is attached to these minutes. After the paper was read Dr. Lijinsky commented that he strongly disagreed with many of the statements in it. Dr. Mussman replied that he thought there would be some differences of opinion, but the paper reflected the thoughts to that time, and there would be opportunity to comment further through the afternoon.

Dr. Jacobson started the discussion by pointing out that nitrite was totally unnecessary in some foods such as "toddler meals." He said there was a need to examine other products so that judgment could be made as to whether they were acceptable or not. He also spoke of other chemical substitutes such as sorbates, and preservation with salt.

Dr. Greenberg replied that there was no denying that other methods of preservation could provide equal safety against the botulism hazard, but that the products would not be frankfurter or luncheon meat--they would be different products. For his part, the industry had been producing safe products for 50 years, which were also organoleptically pleasing to the consumer. He urged care in rushing off into other systems before they had been thoroughly checked out.

The question of product wholesomeness and safety was brought up and although products without nitrite would certainly still be considered wholesome, the question of safety through the distribution channel would warrant serious consideration.

Dr. Lijinsky stated that Dr. Greenberg's approach was very reasonable but ommitted the fact that nitrite is a very dangerous substance, and particularly dangerous in the form in which it occurs in meat because of the high concentration. He considered the risk from nitrite as a contributor to cancer greater than the risk from botulism. Dr. Greenberg disagreed.

Dr. Lijinsky reminded Dr. Greenberg that thousands of people die of cancer every day, and no one knows why. Dr. Greenberg responded that thousands of people do not die of botulism every day, and we do know why.

Dr. Mirvish stated that it was wrong to automatically label nitrite the villian. Nitrite itself is not carcinogenic, and the worry, therefore, is preformed nitrosamines or in vivo nitrosation in fried bacon. Nitrosamines in meat should only be looked at in terms of the total environmental exposure.

Dr. Keating questioned Dr. Jacobson's statement that sorbate could replace nitrite since the preliminary work presented to the Panel to date showed that it had to be used in combination with nitrite for total effectiveness, and the mutagenicity experiment could not be duplicated entirely. Dr. Jacobson suggested that USDA should be doing some additional work as well.

Ms. Zawel expressed her concern that radical changes in processing, which would require changed handling practices in the home, were extremely hazardous. The need not only for investigation in model systsms, but impact within the context of consumer usage.

Dr. Jacobson said that an all-out effort was the need to reduce total nitrite intake from all sources. He went on to repeat that the committee should probe all possible alternatives and examine samples of products produced under different systems to determine safety and acceptability. Works of that type have not been done.

Dr. Schaffner saw two issues; one, the hazard of botulism and an assessment of the risks; and two, what effect reduction of nitrite in meat would have on the total diet. Eighty percent of nitrite ingestion comes from saliva. He agreed that it would be advantageous to have samples produced for Panel evaluation.

Dr. Edwards mentioned the work done to establish the amino acid requirements of man and likened it to multiple factors involved in botulinum inhibition. She wondered whether a similar design would be appropriate. Dr. Greenberg replied that there was a certain minimum amount of nitrite required to show any inhibitory effect upon any number of spores, and that amount is somewhere between 50 and 100 ppm. As the spore load increases the amount of nitrite needed increases, but there is no low number which requires less than 50-100 ppm. Dr. Schaffner suggested that the Panel should review the work the American Meat Institute had done over the past 7 years. He believed that 100 ppm was the breaking point insofar as safety was concerned.

Dr. Greenberg agreed, and also felt that the Panel should see and tast samples.

Dr. Keating expressed some doubt about the value of samples, hoping that the Panel would not go through another experience like the spoiled Lebanon Bologna that was presented several years ago. He also pointed out to Dr. Edwards that the amino acid experiment to which she referred had taken 10 years to complete, and that to experiment similar for the nitrite Panel would take at least 10 years plus enormous amounts of time and money. The public would have to support such a study, and at the end it would still not be known whether any human had or will die of nitrosamine ingestion.

Dr. Mirvish asked about the possibility of less nitrosamine formation if the bacon were less fatty; asked about nitrosamines in the air above the frying pans; and suggested that lowering the pH would probably favor increased nitrosamine formation.

Dr. Wasserman said that it was not yet known whether the collagen in fat was involved in nitrosamine formation but some 80 percent of the nitrosamine volatilizes into the air above the frying bacon.

Discussion then took place about the possibility of in vivo formation of nitrosamines. Dr. Lijinsky said that in his view the ingestion of cured meat containing 100 ppm of sodium nitrite gave an immediate charge of 10 mg. of nitrite to the stomach and that in his view, that amount was of utmost importance.

He objected to the average values and the amounts cited as coming from saliva being given the importance they were. The danger to him was immediate ingestion of nitrite and amines. He did not see how the Panel would dismiss the nitrite in meat as being less important than that from other sources.

It was pointed out that there are dramatic rises in nitrite in the saliva after ingesting certain vegetables. The conditions produced were similar to those cited by Dr. Lijinsky. He, however, said that saliva is secreted continuously. Dr. Keating took issue with the statement stating that there were definite peaks and valleys.

Dr. Lijinsky stated that although the amount of nitrite in cured meats might be a small proportion of the total nitrite entering the G-I tract, it cannot be dismissed as insignificant because it would come in a relatively concentrated amount, and the possibilities of contact with an amine with resultant formation of nitrosamines could be increased.

Ms. Zawel requested that the Panel discuss alternative processes to curing with nitrite.

Dr. Keating responded by discussing irradiation, which had been considered by the Panel early in its deliberations, but not further discussed as it is not permitted by FDA to be used with human food.

Dr. Wierbicki of Natick Laboratories briefly described their research on irradiation of meat. He finds that irradiated cured meats still need a 1:1 nitrite/nitrate mixture, at about 75 ppm for ham and corned beef and 50 ppm for bacon, to retain color. It is not needed to protect against botulinum. Dr. Wierbicki urged that nitrite/nitrate mixtures be allowed for use in country hams, fermented sausages, and irradiated meats.

In response to a request from Ms. Zawel, Dr. Wierbicki described the animal feeding studies being done by Natick on mice, rats, and dogs to demonstrate safety to irradiated meats.

Dr. Schaffner pointed out, and Dr. Wierbicki confirmed, that meats to be irradiated must first be frozen to avoid formation of off-flavors. Dr. Schaffner expressed concern about energy requirements for the civilian population because of the freezing, but Dr. Wierbicki indicated there would be energy savings in distribution and storage because the irradiated product can be defrosted and stored without refrigeration.

Dr. Greenberg stated that using heat to destroy C. botulinum would result in a product different in looks, taste, and feel from current product, because increasing heat renders out more material. This effect occurs irrespective of the level of nitrite in the product. Minimum levels of nitrite are required to provide the organoleptic characteristics Americans are use to, but are considerably less than the amounts necessary for botulinum protection.

As a result of Dr. Greenberg's statement that if temperatures are right, the botulinum organism can grow and produce toxins in previously frozen product, Ms. Zawel stated her conclusion that freezing had the greatest potential for consumer error, at the point in the distribution chain where Government has no control.

Dr. Droudt pointed out that freezing could concentrate the nitrite and therefore could increase the rate of nitrosamine formation.

In response to a question from Ms. Zawel, Dr. Greenberg said that toxin is not formed in fresh meat or poultry prior to organoleptic change, but adding salt makes for problems. There is an area he called the "gray zone" from about 6 1/2 to 8 percent brine where the organism can grow and produce toxin without organoleptic change.

Dr. Keating stated his reluctance to spend a great deal of consumers' money to find out how much it costs to refrigerate all food, when the real risk from nitrosamines is unknown.

Dr. Mussman brought up the subject of drying meat down to a water activity that would prevent outgrowth of botulinum. Dr. Greenberg commented that solid pieces of meat, in order to get all of the product below the danger level, must be dried to a point where they are now very

acceptable organoleptically, according to experiments done to date. He and Dr. Wierbicki both reported no success in using products such as polysaccharides to bind water so that it was unavailable to organisms.

Dr. Mirvish asked if nitrite is uniformly distributed in cured meat. Dr. Wasserman responded that it was distributed about 60 to 40 in lean vs. fat. Dr. Keating pointed out that different techniques of curing resulted in differing homogeneities in product.

In response to a comment by Dr. Jacobson that salt could apparently substitute completely for nitrite in country-cured hams, Mr. Johnston said that the experiments on country hams in the 9th meeting did not demonstrate that there is no problem, because the hams were dried before the botulinum spores were added. However, Dr. Greenberg pointed out, the recommendation was made that nitrite and nitrate could be dropped from 640 and 2,100 ppm respectively to 100 and 300 ppm. Ms. Zawel stated that salt intakes are too high and that she was not sure salt-curing was a viable alternative to nitrite.

Dr. Schaffner reported that additional feeding studies would be required to demonstrate safety of parabens. Although parabens are GRAS, the increased use of them for meats would require added testing before they could be used in these much greater amounts.

Subcommittees were appointed to consider in detail some problems to be discussed at the next Panel meeting. These subcommittees are:

1. Acceptability of other chemical preservatives--Keating, Lijinsky, Jacobson, and Schaffner.

2. Selection of products to be reviewed by the Panel--Greenberg, Mirvish, Sundberg-Werner, and Edwards.

3. Impact on energy requirements, environment, and economics in changing processing--Wasserman, Falk, and Zawel.

Subcommittees were authorized by Dr. Mussman to invite consultants. Funds would be made available to pay travel costs.

Dr. Mussman raised the following questions for the Panel to consider:

(1) What should be the Panel's role in the future?

(2) Would you recommend doing things differently then we are doing them today?

(3) What should be the Government's role?

Dr. Edwards requested that the problem of nitrosamines in bacon or ham fat, which may be used in seasoning vegetables, be studied at the next meeting.

Dr. Mussman indicated that the carcinogenic effects of nitrite, nitrate, and nitrosamines would be reviewed at a future Panel meeting. It was suggested that presentations be made by Dr. Newberne or Dr. Shank from MIT, Dr. Lijinsky, Dr. Mirvish, and Dr. Preussmann from Germany.

Dr. Schaffner reported results of recent market-basket surveys for nitrosamines in bacon. He reported values for nitrosopyrrolidine ranging from 4 to 75 ppm. Previous analyses showed ranges from 5 to 20 ppm. Mr. Fried reported on probable levels of nitrite and erythorbate or ascorbate being pumped into the bacon reported on by Dr. Schaffner.

The meeting was adjourned at 4 p.m.

The Twelfth Meeting - June 1977

Dr. Mussman opened the 12th meeting of the Secretary's Expert Panel on Nitrites, Nitrates, and Nitrosamines at 9:30 a.m. on June 27, 1977. He introduced Dr. William Lijinsky, who gave a presentation on the carcinogenicity of nitroso compounds. The text of Dr. Lijinsky's talk is attached to these minutes as is that of the next speaker, Dr. Sidney Mirvish, who spoke on recent relevant experiments in the nitrosamine field.

General questioning by the Panel members followed the presentations. Dr. Wasserman asked about the significance of the low levels of nitrosamines, and Dr. Lijinsky answered by stating that the highest levels had to be considered. This was a standard protocol in safety testing. He pointed out that those who advocated the necessity of nitrite as protection against botulism based their position on studies which used large spore doses.

Dr. Falk said that there is an area where a no-effect level could be considered. Dr. Keating asked if there was any evidence of synergistic effects with other carcinogens that could make even such small levels dangerous. Dr. Lijinsky replied that Schmahl in Germany had taken several different carcinogens at low levels and when put together, tumors were formed beyond the level expected. The study was not conclusive. Dr. Falk said that there appeared to be some synergy between saccharin and nitrosamines in the formation of bladder tumors.

Dr. Jacobson was disturbed by Mr. Mirvish's remark that if background levels of nitrosamines were found, they should be accepted. He felt that every effort should be made to reduce total exposure. He also questioned Dr. Lijinsky as to whether the exposure to residual nitrite should be reduced in every way possible. Dr. Lijinsky agreed that it should.

After the noon recess, the Panel discussed the risks of nitrosamines in bacon. As background, Dr. Mussman said that the Panel had recommended a reduction of ingoing nitrite from 200 ppm to 156 ppm for most cured meats, but that after that meeting, information was made available that led to a recommendation that a target of 125 ppm of nitrite be stipulated for bacon with mandatory use of 550 ppm of ascorbate. A proposal was issued, but as of this date, 200 ppm remains in the regulations. He called for Panel discussion assessing the risks of bacon and possible recommendations for use of nitrite in bacon.

There was a brief discussion of the methodology and the limits placed upon how small an amount of nitrosamine can be confirmed. It was followed by an exchange of views on the exact amounts of nitrite now being used in bacon. The variability of the ingoing amounts and reasons

for that variability were advanced. Dr. Jacobson asked why no minimums were specified in the regulations, and he was told that the proposal did set a minimum/maximum.

The question of the exact amount of nitrite needed to prevent botulism was next addressed-a question that had been thoroughly discussed at previous meetings. There was no exact answer available. Dr. Keating pleaded that the Panel stop what appeared to be a countering of a one-sided proposal with another one-sided proposal. He asked that instead of polarizing, they try to come to some reasonable point from which recommendations of a sound nature could be made and be used as a starting point for further information gathering.

Dr. Jacobson introduced the idea of a warning on labels to the effect that frying causes the formation of carcinogens. Mrs. Zawel said that her investigation indicated that warning labels were not enough. Drs. Lijinsky and Keating agreed with her.

Dr. Schaffner made a suggestion that USDA proceed to implement its regulation on bacon and, if necessary, modify it later. Dr. Lijinsky disagreed. Dr. Jacobson also disagreed and said that if the 120 ppm of nitrite/550 ppm ascorbate regulation was to be used, it should be an interim regulation for only 1 year, after which nitrite would be banned unless it could be shown that it in itself was harmless and no nitrosamines were formed.

Mrs. Zawel said that the work done by her committee indicated that the 1-year limit was impossible to live with.

The consensus of the Panel was that it was too soon to make any commitment, and that the motion should be tabled for a later date.

Dr. Mussman then called for the reports by the three subcommittees which had been appointed--that on samples of product preserved by heat, salt, and lowered water activity; other chemical preservatives; and economic, environmental, and energy impacts associated with alternatives to nitrites. Those reports are attached to these minutes.

The meeting was adjourned at 4 p.m. with the announcement that the next meeting would be held on July 25 and 26.

The Thirteenth Meeting - July 1977

The meeting convened at 9:30 a.m. on July 25, 1977. Mr. Fried introduced Dr. Robert Angelotti, recently appointed Administrator of the Department's Food Safety and Quality Service (FSQS). Dr. Angelotti replaced Dr. Harry Mussman as vice-chairman of the Panel. Dr. Mussman had served as vice-chairman and executive secretary of the Panel since its inception.

Dr. Angelotti welcomed the Panel and the audience, and mentioned that the Panel had accomplished a great deal, but there was yet work to be done. The Department's Assistant Secretary, Mrs. Foreman, had engaged in correspondence with the Commissioner of FDA, questioning the status of sodium nitrite in poultry as a color and food additive.

Dr. Kennedy of FDA responded that in the view of his Agency, sodium nitrite in poultry is both a food and color additive, although primarily a food additive. FDA is considering issuing a Federal Register announcement that would state that upon submission of a formal petition for the use of sodium nitrite as a food additive in poultry, they would consider the conditions necessary to allow for its interim use and those for a final safety evaluation and the amount of time appropriate for generating longtime toxicity data.

The U.S. Department of Agriculture (USDA) intends to take a similar position for red meat, with the primary issue at this time being the preformation of nitrosamines. He asked the Panel to read the exchange of correspondence between Mrs. Foreman and Dr. Kennedy, and to consider the contents carefully in preparing their final recommendations before the expiration of their charter.

The meeting continued with formal presentations by Dr. Preussmann, Institute for Experimental Toxicology and Chemotherapy, Heidelberg, Germany, and Dr. Newberne, Department of Nutrition and Food Science, Massachusetts Institute of Technology. The text of their talks are contained in a transcript of the meeting, available at the office of the Department's Hearing Clerk.

Dr. Preussmann summarized his talk by saying that:

1. Nitro compounds are among the most potent chemical carcinogens we now know.

2. Technically, these compounds product malignant tumors in experimental animals, in practically all of the vital organs.

3. The tumors are similar in almost all cases to pathohistological tumors known from human pathology.

4. Doses necessary for tumor initiation are rather low.

5. He had presented the multi-generation effect from experiments done by Tomatis.

6. There are no data that the nitro compounds are carcinogens in man, although the evidence is strong that they would be.

He closed with the caution that man must look at his entire environment, since it is probably cumulative total exposure which is important, rather than single carcinogen dosages.

Dr. Newberne summarized his work on feeding rats, diets of varying amounts of nitrite and morpholine, alone and in combination. He stated that the study proved that a carcinogen was being formed in vivo although they have not been able to isolate it because of the speed of nitrosation. They are now performing an indepth study of the effects of nitrite alone, but the program is only 50 percent completed, so no conclusions can be drawn.

Dr. Preussmann remarked upon the importance of making nitrosamine analyses on test diets. He stated that none in Germany were found entirely free, and some ranged as high as 76 ppb.

Dr. Edwards suggested that USDA take the lead in research needed to determine the combined effects of the environment and ways to combat those which were undesirable. Dr. Angelotti said that although it was appropriate for the Panel to discuss needs for future research, their designated task was to make recommendations concerning the continued use of nitrite in cured meats.

After lunch, a brief inconclusive discussion was held concerning the incidence of stomach cancer in areas where the nitrite content of the water was high. Also, briefly mentioned was the need for a study of vegetarians with their supposedly high nitrate intake. Epidemiological evidence is too sketchy at this point for firm conclusions.

Various members of the Panel spoke about methodology now being employed and the drawbacks encountered. Although claims are made that 0.1 ppb of nitrosamines can be detected, all agreed that none are reported unless they can be confirmed by mass spectiophotometry. Newer instrumentation gives promise of eventually allowing a monitoring system for the presence of nitrosamines.

Dr. Birdsall of the American Meat Institute then presented the results of two of their studies. The first indicated that although nitrosamines were still being found in their market survey, there was a marked reduction and even elimination of nitrosamines in those samples cured with the recommended 125 ppm of nitrite/550 ppm ascorbate versus those cured with higher nitrite and/or lower ascorbate levels.

He also reported on residual nitrite in cured meats at various times after production. Although nitrite is fairly high soon after production, it shows a sharp drop within 7 to 14 days. It will then contine to drop off very slowly. Canned products have a slower rate of decline than other products.

A rather heated discussion then took place among the Panel members as to the course to be taken--"safety" from botulism in terms of specific numbers of botulinum spores, "safety" from preformed nitrosamines, or "safety" from in vivo formation of nitrosamines by reduction in the amount of residual nitrite.

Dr. Angelotti pointed out to the Panel that they as a Panel could not accomplish many of the ideas they were expressing; only the Department could. The Department was looking to the Panel for agreement on recommendations as to what the Department should do if emphasis had to be placed on alternate processing procedures, or what had to be done to remove the substantive question of safety. Those questions should and must be addressed at later meetings before expiration of the Panel's charter. He said that he expected the Panel to reach a consensus view and to answer some fairly specific questions. Should residual nitrite be allowed and how much? Should nitrite be banned in bacon, and if so, why?

The Panel then entered into a discussion which was a repetition of several which had gone before. The numbers of botulism spores which had be be guarded against, the exact amount of ingoing nitrite needed to guard against botulism outbreaks, the amount and role of residual nitrite, the effort which should be made to find substitutes for nitrite, and the relative risks of botulism versus cancer. As before, the discussion was inconclusive.

Dr. Schaffner then reported that the Monsanto study on the use of sorbate to replace or supplement nitrite had run into some unexplainable problems, and was in the process of being done over. A report would hopefully be ready at the end of August.

The Panel then adjourned for the day to reconvene at 10:30 the following morning. Earlier in the morning, the Panel had examined samples of canned luncheon meat, frankfurters, bacon and irradiated ham produced at varous cooking temperatures, various water activites, and from zero to 150 ppm of nitrite. A list of those samples is enclosed. The Panel then gave their opinions as to the acceptability of what they had seen.

They were in general agreement that the lowest levels of nitrite used could still produce an acceptable color. They also agreed that they were unable to evaluate the safety of those low amounts of nitrite. They differed in their opinions as to which might be organoleptically acceptable. There was also disagreement as to whether no nitrite at all produced a product which was acceptable.

Dr. Angelotti pointed out that he doubted whether the Committee members present, looking at the array of samples subjectively, could arrive at any conclusion. He hoped, however, that they might point out some avenues which showed promise and would bear further investigation from the Department. One such was pre-fried bacon with 30 or 40 ppm of nitrite. The color, flavor, and texture seemed acceptable--frying lowered the water activity to where the product was safe from botulism, and the low level of nitrite indicated the good possibility that preformed nitrosamines would be absent. Dr. Angelotti wondered whether a frozen bacon with no nitrite would be acceptable. Ms. Zawal and some members of the audience expressed doubts as to the safety of such a product because of the long time in distribution channels and the possibility of mishandling.

Dr. Angelotti concluded that segment of the meeting by stating that certainly, the Panel could make any recommendations it wished. He asked, however, that the members carefully consider the implications of their recommendations. For example, he would find in unacceptable if they said, "In our opinion, the bacon ought to be manufactured at 30 ppm, 8 percent salt, because it looked OK to us." The reason for its unacceptability was that it would require a change in the regulations which would require an economic impact analysis. That analysis could determine that the economic impact was larger than the rules laid down for allowing regulatory change. That is why it was important for the Panel to consider all ramifications of what it suggested.

Dr. Angelotti went on to say that the primary charge of the Panel was to review the health question relative to the continued use of nitrites and nitrates. He expressed the thought that the Panel had approached the problem in a deliberate manner and was now about to conclude their deliberations. All information available had been presented to the Panel. The charter of the Panel expires on September 22, 1977. He asked that the Panel consider certain issues and directed its attention to what had transpired between FDA and USDA to this point. There was an exchange of correspondence between Assistant Secretary Foreman and Dr. Kennedy, Commissioner of FDA, who established FDA's position that nitrites and nitrates in poultry are both food additives and color additives. Their continued permitted use would depend upon promulgation of a regulation under the FDCA for a food additive. Such an interim regulation would give the industries involved time to generate the long-term chronic toxicological data needed to support such a regulation. During that period, action would not be taken against cured poultry products provided that industry submitted data showing there were no preformed nitrosamines in the products.

Dr. Angelotti pointed out that nitrites' safety has been questioned. In red meat products, it is <u>not</u> a food additive by legal definition, and therefore, is not subject to the food additive amendment. Legally, it is not, because certain exemptions were made for products sanctioned by

USDA and FDA prior to the passage of the amendment. Nitrite falls into this category. This will not excuse USDA from exercising its moral and ethical commitment to deal effectively with substantive questions of safety. USDA will do something about nitrosamines.

Mr. Butler then made several pertinent remarks, summarizing the situation to this point and added several issues to those listed by Dr. Angelotti.

He wanted the Panel and those in the audience to know that I think the Secretary's office understands the serious nature of both sides of the issue.

On the one hand, there is the potential cancer risk. On the other hand, you have the potential botulism risk.

There is no doubt that those are serious risks on both sides. He said that if the issue came down to only those two issues, those two concerns, the job of the Panel and the job of us reviewing the Panel's recommendations would be easy.

The third factor that comes in--he wanted those seated in the audience and the Panel to understand this--the third factor that comes into play is the issue of consumer acceptance.

In his mind, he has it broken down into the cancer risk and the botulism risk, plus an element in there of consumer acceptance.

At the same time, he thought that everyone will also accept the fact that is is a serious public health issue, and it is one with which we should address ourselves with particular clarity.

In that regard, he would appreciate the Panel viewing the alternatives to the present practices.

I am certain that one alternative will be and should be some recommendation on the different levels of ingoing nitrite in cured meat products, including bacon.

I would also like to see a complete evaluation, and that includes a knowledge and remembrance of what has gone on here in the last couple of days, of the different processing practices that can be employed; and possible different distribution procedures, different handling procedures.

I would like to have a reasonable evaluation of a recent research study on ascorbic acid, for example, or potassium sorbate, or if there are other blocking agents that are now being tested within industry of which the Panel is aware. I would like to know those also.

I am saying that not as an indictment of industry at all. I hope that that is well understood, but only to help me understand an issue which I think you can clarify for me by giving me those alternatives.

Next, I think Bob has mentioned this. I would like for the Panel to look closely at those products in which no botulinal inhibition is necessary.

For example--I think this has been mentioned throughout--there are certain sterile cooked products, or certain toddler foods that I understand don't need nitrite added for botulinal protection. I would like to know those types of products.

As Bob mentioned, that request of the Panel is consistent with the exchange of letters that I think you will find in the packet between Commissioner Kennedy and Secretary Foreman.

That is, to identify and eliminate all nonpreservative uses of nitrates and nitrites except where the safety of other uses such as color and taste can be documented.

Let me go back over that once again.

The exchange of letters between Carol Foreman, Assistant Secretary for Food and Consumer Services, and Commissioner Kennedy who agree that the goal of FDA and USDA with regard to nitrites and nitrates in poultry products should be--this is one of the goals--should be to identify and eliminate all nonpreservative uses of nitrates and nitrites except where the safety of ther uses such as color or taste can be documented.

The next request I would have of the Panel--and this is one I think can be answered quickly because I don't think there is an answer at the moment--I would like to see a review, or a listing, of the research which has been done on what happens in the interaction of nitrite with the botulinum spore.

Dr. Angelotti then asked the Panel to go on to a consideration of how best to get together and prepare a report. At this point, it was decided that the Panel would meet in the afternoon and decide upon procedures and assignments leading to a final report. Due to a procedural error, that afternoon session was closed to the public and, therefore, those proceeding were scratched from the record.

Alternatively, the Department, upon learning of its error, sent out a list of issues (available to the public) to each Panel member. The Department suggested that each member address certain issues in which he or she had expertise and to address any of the other issues as desired.

They were to make their reports available at the August 17 meeting, at which time, in open session, the method by which a final report would be put together would be discussed.

The Fourteenth Meeting - August 1977

Dr. Angelotti opened the proceedings by apologizing for the procedural error committed at the last meeting, which seemingly deprived the public of participation. To rectify that situation, he explained the manner in which the present meeting, future meetings, and the writing of the final report would take place. Members of the Panel were requested to prepare reports individually in areas where they had particular expertise and, additionally, were asked to comment on any of the other eleven issues identified.

The Executive Secretary was then going to collate the various opinions as expressed at the day's meeting and send them to the members. At the next meeting, hopefully, agreement would be reached on a recommendation that could be made on each of the issues. A final draft of the report would then be prepared and if endorsed by the Panel, submitted as a final report to the Secretary.

Dr. Angelotti mentioned the reports that were made available to the Panel since the last meeting and said that they would also be available upon request to the public.

The reports were:

1. A bibliography of available research on the role of nitrite as an anti-botulinum agent.

2. The final report of subcommittee three on economic analysis of a ban on the use of nitrite.

3. A report on the occurrence of nitrosamines in cured meats in the United States prepared by the American Meat Institute.

4. A report from the Lebanon Bologna Institute on the results from a safety and organoleptic viewpoint of removing nitrate from the curing process of Lebanon Bologna.

5. A paper on "Meat Curing and the Issues of Cancer, Botulism, and Consumer Acceptance," prepared by Dr. W. Lijinsky.

6. A report of nitrosamine occurrence in bacon, and another on residual nitrite in cured meat in the market, prepared by the American Meat Institute.

7. A paper describing experimental protocols to be used for measuring the effectiveness of alpha tocopherol as a nitrosamine blocking agent.

8. A list of the products prepared for the Panel's examination at the last meeting.

9. A report on work done in Canada on long chain acetals of ascorbic acid as blocking agents against nitrosamine formation.

Dr. Angelotti then read into the minutes the eleven issues which were to be addressed by the Panel and suggested that each be addressed, in turn, by the Panel. The minutes would indicate the suggestion or suggestions for recommendations made on each by the Panel. These would then be collated by the Executive Secretary and sent out to the Panel members. At the next meeting, they would attempt to arrive at a single Panel recommendation based on modifications of the suggested responses.

The issues are as follows:

1. Residual nitrites - safety vs. minimal levels for organoleptic acceptance.

2. Preformed nitrosamines - Volatile.

3. Preformed nitrosamines - Nonvolatile.

4. Evaluation of FDA position on nitrite in poultry, in relation to the position that USDA should assume relative to nitrite in cured meat.

5. Interim and long term recommendations concerning bacon with respect to items 1-4 above.

6. Interim and long term recommendations concerning other cured meats in relation to items 1-4 above.

7. Additional resource information or economic and technical feasibilty information necessary to formulate and/or implement long term recommendations.

8. A complete evaluation of alternatives to nitrite usuage, including alternative processing, distribution procedures, handling procedures, and any chemicals or other agents presently under consideration. Please give a complete evaluation on the merits of ascorbic acid, potassium sorbate, or any other blocking agents now under consideration.

9. A determination of products in which no botulinal inhibition is necessary. For example, is there a need for botulinal inhibition in such products as toddler foods or other sterile cooked products? These products should be identified specifically. The object of this evaluation is to determine the amount of nitrite to achieve color and taste only. This approach is consistent with the exchange of letters between

FDA and USDA which say that both agencies should, among other things, identify and eliminate all nonpreservative uses of nitrates and nitrites, except where the safety of other uses (such as color or taste) can be documented.

10. A complete review of the research data on what happens within the interaction of nitrite and the botulinal spore.

11. Are there any products, such as Lebanon Bologna, where the information requested by the Panel has not been submitted. In other words, does the Panel feel that there are any companies or any product which have not been evaluated as extensively as the Panel might have liked?

The collated responses are as follows:

Issue 1 - Residual nitrites and the question of safety versus minimal levels for organoleptic acceptance. See Table 1.

Issues 2 and 3 - Preformed volatile and nonvolatile nitrosamines.

(a) Nonvolatile nitrosamines cannot be adequately analyzed for at this time and therefore it is difficult, if not impossible, to make a recommendation about them. What is known leads to the belief that as a class they are noncarcinogenic or very weakly so.

(b) Volatile nitrosamines are potent carcinogens in laboratory animals and lead to the strong belief that they are carcinogenic in man.

1. No product should be sold if it contains a volatile nitrosamine.

(2) Dose response studies lead to the belief that values of 10 to 20 ppb are not harmful over the course of a lifetime at normal intakes and therefore no action may be necessary.

(3) Low levels may not be harmful in themselves, but because of the total dietary impact from all foods, every effort should be made to eliminate them.

Issue 4 - An evaluation of FDA's position on poultry and its relation to the position USDA should assume on nitrite in red meats.

(a) The inference was made that USDA should do the same in the interest of uniformity.

TABLE 1

Canned Cured ----- Perishable	Shelf stable	Comm. sterile 5/	Bacon	Cooked Sausages	Other Pickle Cured 6/	Dry Cured Cuts 6/	Ferm. Saus.	Infant Foods	
INGOING									
156	156	50	125	100	156	1/ 300 NO3 100 NO 2	100	0	(a)
156	156	50	125	120	156	300 NO3 100 NO2	100		(b)
60	60	60	60	60	60	60	60		(c)
156	156	0	80-120	100		300 NO3	300 NO3	0	(d)
			125						(e)
RESIDUAL									
75 2/ 125/75	75 2/ 125/75	25 50/25	50 2/ 80/50	50 100/50	75 2/ 125/75		50 50/50	0	(a) (b)3/
20-25	20-25	20-25	20-25	20-25	20-25	20-25	20-25		(c) (d)4/

1/ Only after testing on commercial basis.
2/ One week after manufacture.
3/ X/Y, where X is zero time after processing, Y is 7 days later.
4/ Control ingoing closely, no need to control residual since it will go down as a function of time, temperature, type of process, product handling practices, etc.
5/ See alternate recommendations under Issue 9.
6/ See alternate recommendations under Issue 11.

(b) The suggestion was made that there are some inherent differences in the economic impact of regulations dealing with nitrite in poultry versus those in red meat that should be considered by the Panel. The impact would be especially great on the small producer.

Issue 5 - Interim and long term recommendations concerning bacon.

(a) Impose a further stipulation that after a given interval, the situation be re-examined and if necessary and safe, further reductions be made in the final recommendations agreed to by the Panel.

(b) A mixture of sodium and potassium chloride be used in order to reduce sodium intake. (Dr. Jacobson to supply reference.)

(c) A warning label be placed on bacon packages similar to "Notice: cancer-causing chemicals may form when this bacon is cooked."

(d) Pre-fry bacon.

Issue 6 - Interim and long term recommendations concerning other cured meats. (See Table 1).

In addition to provisions of Table 1:

(a) Add a time limit to bacon "until June 30, 1978."

(b) Add a time limit "until June 30, 1978," to cooked sausages and canned chopped ham.

Issue 7 - Additional resource information or economic and technical feasibility information necessary to formulate and/or implement long term recommendations.

(a) Other than a restatement of the massive impact a radical change in the production of cured meats would have on consumer eating habits and agricultural economics, nothing new was offered.

Issue 8 - A complete evaluation of alternative methods of preservation, processing, handling, and distribution.

(a) Dr. Rubin of Canada Packers presented a paper on long chain acetals of ascorbic acid as a blocking agent. The results indicate that:

(1) Several in the experiment give a 95 percent reduction in nitrosamine formulation.

(2) They have no organoleptic effect.

(3) The acetal is best applied to the bacon in oil, but the sodium salt in an aqueous solution is also effective.

(4) The acetal, although most effective at the 1,000 ppm level, is also 80-90 percent effective at a 250 ppm level.

(5) The experimental method of application is not commercially feasible.

(6) They are not approved food additives, and no long term toxicological work has been done, although being derivatives of ascorbic acid and long-chain fatty aldehydes, they may well prove to be innocuous.

(Dr. Angelotti thanked Dr. Rubin for adding to the general knowledge of the Panel, but pointed out that because of the length of time needed for toxicological studies--a minimum of 23 years--the information was of no immediate value in terms of recommendations that could be made by the committee.)

(b) Alpha-tocopherol in conjunction with ascorbate seems to have an inhibiting effect on nitrosamine formation.

(c) Irradiation - defined as a food additive and not approved at this time.

(d) Combinations of sorbate and nitrite should be investigated.

(e) A modest increase in salt may allow a decrease in the use of nitrite.

(f) Precooking shows some promise.

(g) None of the chemical alternatives have been subjected to the scrutiny given to nitrite and nitrosamines over the past several years and may be more dangerous to human health. Caution is advised in moving hastily.

Issue 9 - A determination of products in which no botulinal inhibition is necessary; for example, sterile canned foods. (See Table 1.)

(a) Ban cured meats in all infant, junior, and toddler foods which are sterile processed.

(b) Ban cured meats in baby foods, but allow enough nitrite in other canned sterile products to produce color and flavor characteristics.

(c) Ban cured meats in baby foods but allow nitrite in other sterile products if the processor can:

(1) demonstrate need and efficacy of the level of nitrite requested, and

(2) demonstrate that that amount would not increase the risk of nitrosamine formation in the food or in the stomach.

(d) Limit nitrite to a maximum of 50 ppm if added only for color.

Issue 10 - A complete review of the research data on what happens within the interaction of nitrite and the botulinal spore.

The paper submitted to the Panel by Dr. R. Lechowich was accepted as supplying the information requested. (See Appendix F.)

Issue 11 - Are there any products where the information requested by the Panel has not been submitted?

(a) Several varieties of fermented sausages and dry-cured products have not been evaluated, but a basic target level should be set--100 ppm of nitrite for fermented sausage, both dry and semi-dry, and 100 ppm nitrite and 300 ppm nitrate for dry-cured products. Producers who want to use more must present data to substantiate their needs.

(b) Don't take arbitrary action on those products. They have been sold without need for refrigeration and as such are consistently "abused." Until safety of reduced levels is demonstrated, don't change. Perhaps the Government needs to generate that information rather than the small producer.

(c) (b) is not valid because it is the producer's responsibility to generate the required types of controls or information when substantial questions of safety arise.

A discussion was then held on times for the next meeting and preparation of the report. It was decided that:

1. A draft final report including the Panel's collated response to the issues would be prepared and sent to them for evaluation and acceptance within 10 days.

2. The next Panel meeting would be set for around September 15 instead of September 7 as originally thought.

3. The meeting of September 15 would be devoted to a word-by-word review of the draft proposal with a view toward final acceptance

by the Panel of the report and consensus agreement on recommendations on each issue.

The meeting was adjourned at 4:30 p.m.

The Fifteenth Meeting - September 1977

There were no minutes issued covering the fifteenth meeting in September 1977. The meeting was devoted to a discussion of the identified issues. The Panel voted on recommendations; acceptance or rejection being based on majority rule. An unofficial record of those recommendations was issued in lieu of minutes. The Panel edited the unofficial version and these were sent to each member until final agreement was reached. Those final official recommendations appear in this report.

September 21, 1973

SECRETARY'S MEMORANDUM NO. 1826

Expert Panel on Nitrites and Nitrosamines

The Department has a continuing duty to maintain a wholesome and safe supply of meat and meat products. In order to determine whether the present regulations for the use of nitrates-nitrites in processing of meats are adequate to maintain a safe supply of meats in the food distribution system, there is hereby established an Expert Panel on Nitrites and Nitrosamines. Establishment of this Panel is in the public interest in connection with the performance of duties imposed on the Department by law.

The responsibilities of the Panel are solely advisory and include:

1. Assessing available data and information concerning the presence of nitrosamines in foods.

2. Evaluating scientific papers relating to specific problems identified with the use of nitrites in foods.

3. Determining public health significance of nitrite usage in food processing.

4. Determining if satisfactory alternative methods for curing foods are available.

The Chairman of the Panel will be the Assistant Secretary, Marketing and Consumer Services to whom the Panel will report. The Administrator for APHIS will serve as Vice Chairman, and the Deputy Administrator for Scientific and Technical Services will serve as the Secretary of the Panel.

The Secretary will appoint the members and such membership will be rotated if the Panel is still in existence at the end of a two-year term of appointment. Members will be scientists representing the following disciplines: toxicology, oncology, biochemistry, microbiology, gastroenterology, and others.

Support for the Panel in terms of fiscal management, meetings, records, and other Panel activities shall be provided by APHIS. It is anticipated the Panel will meet four times annually and the estimated annual costs are $3,450.00 (travel and per diem) and .5 man years staff support.

The Panel will terminate two years from the date of this memorandum unless its purposes have been fulfilled in a shorter period of time, at which time the Panel will be terminated. If, however, there is a continuing need for the Panel at the end of the two-year period, the Secretary may renew the Panel upon a finding that it is in the public interest to do so.

/s/ EARL L. BUTZ
Secretary of Agriculture

November 12, 1975

SECRETARY'S MEMORANDUM NO. 1826, REVISED

Expert Panel on Nitrites and Nitrosamines

The Department has a duty under the law to see that meat and meat food products distributed in commerce are safe and wholesome. In order to determine whether present regulations governing the use of nitrates and nitrites in meat food products are adequate to maintain a safe supply of meat food products in commerce, the Expert Panel on Nitrites and Nitrosamines is hereby renewed. Renewal of this Expert Panel is in the public interest in connection with the performance of duties imposed on the Department by law.

The responsibilities of the Expert Panel are purely advisory. They will include:

1. Assessment of available data and information concerning the presence of nitrosamines in foods.

2. Evaluation of scientific papers relating to specific problems identified with the use of nitrates and nitrites in foods.

3. Determination of the public health significance of nitrate and nitrite usage in food processing.

4. Determination as to whether or not satisfactory alternative methods for curing foods are available.

The Chairman of the Panel will be the Assistant Secretary, Marketing and Consumer Services, to whom the Panel will report. The Administrator for APHIS will serve as Vice Chairman, and the Associate Administrator for APHIS will serve as the Executive Secretary of the Panel.

The Secretary will appoint members which may include scientists representing the disciplines of toxicology, oncology, biochemistry, microbiology, gastroenterology and others as may be deemed appropriate.

The Panel will meet semiannually, and will terminate September 21, 1977. APHIS will provide the necessary staff support which is estimated to be $14,640 including .5 man-year staff support.

This memorandum will serve as the Charter.

Secretary's Memorandum No. 1826, dated September 21, 1973, is hereby superseded.

J. PHIL CAMPBELL
Acting Secretary

Initial Recommendations

In December of 1974, Dr. Mussman, then Vice Chairman of the Expert Panel, sent a memorandum to Assistant Secretary Feltner containing recommendations made by the Panel. That memo follows:

Subject: Recommendations of the Expert Panel on Nitrites and Nitrosamines — December 4, 1974

To : Richard L. Feltner, Assistant Secretary
Marketing and Consumer Services

Through: F. J. Mulhern
Administrator

During its September meeting, the fifth in the series, the Expert Panel on Nitrites and Nitrosamines finalized recommendations on nitrate and nitrite usage to be made to the Secretary at this time. Accordingly, I am submitting them to you for your consideration and action as deemed appropriate. There are three recommendations, as follows:

1. That use of nitrate salts in the curing process be discontinued in all meat and poultry products, with two exceptions, dry-cured and fermented sausage products. These two product categories will be addressed at a later date when additional data are available.

2. That the level of nitrite salt permitted to be added for curing of meat and poultry be limited to 156 parts per million (ppm) in all processed products, with the exception of bacon and dry-cured products. Recommendation for these latter products will be deferred pending availability of further research data.

3. That the currently permitted 200 ppm residual nitrite salt level be reduced in various product categories to reflect what is achievable with current technology. The Panel believes that 100 ppm in cooked sausage products, 125 ppm in canned cured and pickle cured products, and 50 ppm in canned cured sterile product would be sufficient to maintain product safety. Action on bacon, fermented sausage products, and dry-cured products is deferred until additional research data being developed become available.

It is the consensus of the Panel members that these recommendations are consistent with all safety considerations. Levels of nitrate and nitrite are decreased, thus reducing the consumers' exposure to the potential hazards of nitrosamines, nitrosamides, and related chemicals; at the same time, sufficient levels of nitrite are maintained to protect the consumer against the very real hazard of botulinal poisoning.

The Panel will reconvene at irregular intervals in the future to consider new information as it becomes known. New recommendations will be formulated as needed.

/s/ Harry C. Mussman
Executive Secretary
Expert Panel on Nitrites
and Nitrosamines

In November 1976 the Panel, which then consisted of Drs. Edwards, Greenberg, Keating, Schaffner, Wasserman, and Weisburger, issued the following report.

POSITION PAPER, EXPERT PANEL ON NITRITES, NITRATES, AND NITROSAMINES

During the ninth session, the Expert Panel agreed that it would be wise to issue a summary of their findings and conclusions to that time. They realized that further research and exploration was necessary. They also realized that as new material comes to their attention, revisions and modifications of their position may be necessary. The Panel felt, however, that this document would have real value as a summary of the knowledge available. This position paper represents the consensus of the Panel.

In 1973 the Secretary of Agriculture established an Expert Panel on Nitrites, Nitrates, and Nitrosamines to advise him as to whether the usage of nitrites and nitrates in the curing of meats constituted a public health hazard,--and if so, whether such usage should be modified or prohibited. It was the intent of the Secretary to have represented on the Panel experts in the several scientific areas which impact upon the nitrite question. The Panel members selected were Doctors Cecile Edwards (human ecology), Leo Friedman (toxicology), Richard Greenberg (microbiology), James Keating (pediatric gastroenterology), Aaron Wasserman (chemical microanalysis), and John Weisburger (oncology). Dr. Friedman died on July 6, 1974, and was replaced on the Panel by Dr. Robert Schaffner (food technology).

The Panel was asked to review all aspects of curing meat and poultry products and the various problems which had been identified with this processing procedure. Specific recommendations were to be made wherever appropriate.

To prepare themselves for this task, the Panel decided to review a variety of topics associated with meat curing, starting with its history. The first Panel meeting was held February 8, 1974. Panel members heard from researchers and other scientists who discussed naturally occurring nitrites and nitrates in foods, soil, water, and air; the chemistry of meat curing; the chemistry of nitrosamine formation; the extremely sophisticated methodology associated with nitrosamine analysis; and the potential hazard of botulism associated with meat products. A variety of other subjects was presented at subsequent meetings, including a discussion of the epidemology of certain types of cancer and their possible relationship to diet. All meetings of the Panel were open, and substantial numbers of people attended and frequently participated in discussions of subjects under consideration.

At the fourth meeting of the Panel on July 15, 1974, the members decided they were in a position to make their first recommendations to the Secretary. Based on the information presented to them and a review of the pertinent literature, the three recommendations were:

" 1. That use of nitrate salts in the curing process be discontinued in all meat and poultry products with two exceptions; dry-cured products and fermented sausage products. These two product categories will be addressed at a later date when additional data are available.

2. That the level of nitrite salt permitted to be added for curing of meat and poultry be limited to 156 parts per million (ppm) in all processed products, with the exception of bacon and dry-cured products. Recommendation for these latter products will be deferred, pending availability of further research data.

3. That the current permitted 200 ppm residual nitrite salt level be reduced in various product categories to reflect what is achievable with current technology. The Panel believes that 100 ppm in cooked sausage products, 125 ppm in canned cured and pickle cured products, and 50 ppm in canned cured sterile product would be sufficient to maintain product safety. Action on bacon, fermented sausage products, and dry-cured products is deferred until additional research data being developed become available."

In each instance where an exemption was identified, it was the intent of the Panel to continue to receive new information which would permit the members to make further specific recommendations on these products at a later date.

The Secretary of Agriculture accepted the recommendations. On November 11, 1975, the Animal and Plant Health Inspection Service issued the proposed changes in the regulation for public comment. A summation of those comments was presented to Panel on April 28, 1976.

During the drafting of the proposed regulations, new information came to light which prompted the Department and the Panel to agree that there was a need to address the specific problem of nitrosamine formation in bacon. When the bacon is fried, the nitrite combines with certain chemical components of the bacon to form nitrosamines--most of which are carcinogenic. The one most frequently identified in bacon is nitrosopyrrolidine. Because of this information, the Panel recommended lower levels of nitrite usage for processing bacon and further recommended that maximum permitted levels of ascorbate or isoascorbate be used because ascorbate and isoascorbate have been shown capable of reducing nitrosation in bacon. The American Meat Institute was requested to develop information on what effects reduced nitrite and increased ascorbate/isoascorbate usage would have on the formation on nitrosamines.

At its ninth Panel meeting on November 30, 1976, the Panel evaluated the results of reduced nitrite usage in bacon manufacturing under commercial conditions in a 10-plant full-scale production test. The data showed significant decreases in both the occurrence and levels of nitrosamines. The Panel determined that substantial progress has been made in achieving a nitrosamine-free bacon; however, the Panel felt that efforts toward this goal must continue and, thus, an extension should be granted on the time devoted to this work.

In considering the entire question of nitrite and nitrate usage in meat processing, the Panel has had to consider a wide variety of factors. It would be well to cover the most salient of these factors individually and then try to put them all in perspective. Nitrite (or its precursor nitrate) is added to meats in order to develop the characteristic flavor and color desired by consumers of cured meat products. Nitrite also prevents botulinal toxin formation under certain conditions. The bacterium Clostridium botulinum is a natural contaminant of meat products by virtue of its occurrence in soil and as an inhabitant of the gastrointestinal tract of animals. Aerosols produced during slaughtering operations permit this organism to contaminate meat as they undergo further processing. Viable C. botulinum spores have been isolated from a variety of processed meat products at the retail level. Should these products not be properly refrigerated or otherwise abused, C. botulinum can grow and produce a toxin which causes botulism. Over the years, the use of nitrite in meat curing has performed as a built-in safety factor and thereby significantly protected the public health.

Nitrate occurs in practically all parts of the environment but primarily in water and vegetables. It has a very low toxicity. Nitrite on the other hand occurs less frequently in our environment and is somewhat more toxic. However, even with the latter, relatively large amounts are needed to induce toxic changes in test animals. This includes the development of methemoglobinemia which is also seen in man, particularly in infants exposed accidentally to nitrite. Nitrites have not been shown to be carcinogenic or teratogenic at any dose level, although additional research is being carried out.

Continuing with these factors, it is known that nitrite can combine under certain conditions with secondary or tertiary amines to form nitrosamines. There are two sources from which the human might be exposed to nitrosamines: The first would be preformed nitrosamines, naturally occurring in air, water, soil, or foods. The second would be the result of in vivo nitrosation of amines in the intestinal tract. In the latter case, it has been suggested that nitrites from cured meats pose a significant threat. However, it has been demonstrated that nitrates consumed in the human diet are excreted at high concentrations in the saliva and are rapidly converted to nitrite by bacterial reduction in the oral cavity. It is estimated that the nitrite swallowed in the saliva represents in excess of 80 percent of the total nitrite to which the human is exposed. Solutions to the problem of nitrite

exposure could include things such as reduction of nitrate or secondary amine intake. In both instances serious difficulties would be encountered. A third means would be reduction of nitrite consumed in cured meats; the Panel has made recommendations to accomplish this objective.

After having reviewed both old and new information for the last three years, the Panel has narrowed its areas of public health concern to three: one is the threat of botulism in improperly processed meat products; the second is the problem of nitrosamine formation in meat products; particularly in bacon but perhaps in other meats as well; and the third is the exposure level of the human to nitrites which could result in the in vivo formation of nitrosamines.

The Panel is of the opinion that the botulism threat is a serious one and therefore feels continued use of nitrite in the curing process is warranted. The Panel also feels the nitrosamine problem in bacon cannot be ignored and that concern over its existence is justified, even though the amount of nitrosamine present in bacon is in the parts per billion (ppb) level, and the effects of such small amounts of carcinogens in man and animals are not known. It was further noted, that in most animals, orally ingested nitrosamines of the types present in nitrite-treated meats do not lead to the formation of the type of tumors prevalent in the United States population. Regarding the issue of in vivo formation of nitrosamines, the Panel felt that the ingestion of nitrite, per se, from cured meats did not seem to be a major hazard.

The Panel is thus confronted with the problem of making judgments regarding the continued use of a substance where the choices are not as easily categorized as benefits and risks as might be true with other substances. In most evaluations, the risk generally is defined in scientific terms, whereas the benefit is defined more in terms of social value. In the case under consideration, the Panel is faced with assessing what road to take when there are two risks in the equation: one is the potential hazard from the low levels of a carcinogen and the other is the very real threat or risk of botulism poisoning. In other words, the Panel is making a judgment between two risks in arriving at its current position where one of the risks can actually be considered a benefit.

The Panel feels after lengthy deliberations that the reduced levels of nitrite which they recommend and proposed as a regulation change represent the best approach to this two-edged problem based on knowledge available at this time. The nitrite levels proposed represent a sufficient amount to prevent a botulism problem and similarly represent a reduction which has resulted in extremely low and infrequently occurring nitrosamines in a limited category of products. Further, the reduced nitrite levels have helped decrease the exposure of the human to nitrite itself, thereby lowering the possibility of in vivo nitrosamine formation.

Having said all the foregoing, the Panel does not wish to leave it at that. Rather, the Panel insists that continued research be carried out on the part of the processed meat industry, the Department, and the academic community to further refine the usage of nitrite in the curing process. At the same time, the Panel also insists that further research be undertaken to find substances which could substitute in part or for all of the nitrite currently being used. In the event that such studies continue to demonstrate the need for nitrite in the curing process, the Panel is of the opinion that decisions on the future use of these products might best be left to the consuming public. Given adequate information as to the relative risks involved, society itself should be in a position to make a determination as to its willingness to accept potential risks in its daily life.